Postgraduate Medicine

Volume 19 · Number 4

APRIL · 1956

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

TABLE *of* CONTENTS

Special Issue

The George Washington University School of Medicine and Hospital

GUEST EDITOR: ***Brian Blades, M.D.***

Foreword
CLOYD HECK MARVIN, PH.D. 308

Introduction
WALTER A. BLOEDORN, M.D. 309

The Management of Anticoagulant Therapy by a Simple Blood "Prothrombin" Test
BENJAMIN MANCHESTER, M.D. 311

Pectus Excavatum
BRIAN BLADES, M.D., OWEN GWATHMEY, M.D. AND PAUL C. ADKINS, M.D. 318

Brucellosis and Heart Disease
I. The Shaky Foundations of "Rheumatic" Heart Disease
THOMAS M. PEERY, M.D. 323

Nodular Goiter and Thyroid Cancer
VINCENT M. IOVINE, M.D., WILLIAM S. McCUNE, M.D., WALTER H. GERWIG, M.D. AND ALEC HORWITZ, M.D. 328

Physiologic Basis for Rational Therapy in Chronic Pulmonary Emphysema
JAMES J. FEFFER, M.D. AND JAMES P. MANN, M.D. 332

Side Effects of Antibiotic Therapy
JOHN P. NASOU, M.D. AND MONROE J. ROMANSKY, M.D. 341

Chlorpromazine and Reserpine in Psychiatric Practice
WINFRED OVERHOLSER, M.D. 346

Significance of a Lump in the Parotid Gland
JOHN C. LUCAS, M.D., WILLIAM NEWMAN, M.D. AND CALVIN T. KLOPP, M.D. 350

(Continued on page A-10)

Fractures of the Nose
MAXINE SCHURTER, M.D. AND GORDON S. LETTERMAN, M.D. 354

Local Anesthesia
CHARLES S. COAKLEY, M.D. 360

The Negative Myelogram and Nucleography
HENRY L. FEFFER, M.D. AND HUGO V. RIZZOLI, M.D. 363

Common Injuries of the Knee
CHARLES KECK, JR., M.D. AND JOHN P. ADAMS, M.D. 369

Congestive Heart-failure: Prevention and Treatment
CLAYTON B. ETHRIDGE, M.D. 381

Injuries of the Urinary Tract
F. TURNER REUTER, M.D. AND FREDERICK A. REUTER, M.D. 385

Cancer of the Brain: Newer Methods of Diagnosis and Treatment
JAMES W. WATTS, M.D. 389

Preparation and After-care of Older Patients Requiring Surgical Intervention
CHARLES W. THOMPSON, M.D. 393

Departments

EDITORIALS 397
Overtreated Fractures
Obstetrics As a Science
The Rheumatic Crossroads

"PLACEBO"—Jackson A. Smith, M.D. A-18

YOUR QUESTIONS ANSWERED A-28
Cataract Following Eye Injury
Infected Fingernails

WHAT'S HAPPENING IN MEDICINE Facing A-32-33

FORENSIC MEDICINE A-36
Psychiatric Disturbances Following Trauma and Stress
DANIEL W. BADAL, M.D.

LABORATORY NOTES. Arthur H. Sanford, M.D. A-50

MEDICINE FROM ABROAD A-56

NEW FOR YOUR ARMAMENTARIUM A-84

PRODUCTS BY THERAPY INDICATIONS A-91

THE MEDICAL BOOKMAN A-106

DR. PEPYS' PAGES. Morris Fishbein, M.D. A-134

THE MEDICAL MUSE. Richard Armour A-140

INDEX TO TECHNICAL EXHIBITS A-144

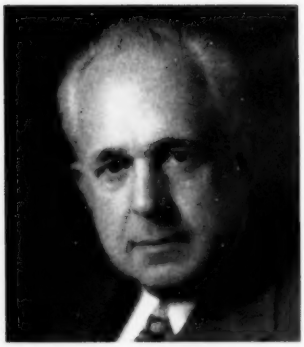
Postgraduate Medicine

SPECIAL ISSUE

The George Washington University

School of Medicine and Hospital

Guest Editor: BRIAN BLADES, M.D.



DR. CLOYD HECK MARVIN

FOREWORD

In terms of medical scholarship the national capital area often has been called "strategic." For students at The George Washington University Medical School, the proximity of various governmental and military installations and special libraries makes possible an augmented program of research, clinical instruction and association.

In addition to affiliation for teaching purposes with the Mt. Alto Veterans Administration Hospital, Walter Reed General Hospital and St. Elizabeth's Hospital, there are faculty-student relationships with federal medical programs and the research activities of such agencies and centers as the U.S. Public Health Service, the National Institutes of Health, the Food and Drug Administration, the Federal Trade Commission, the Atomic Energy Commission, and others.

The George Washington University Medical School not only is privileged to participate in and benefit from all the programs and services already mentioned, but also has access for medical scholarship to the unique collections of the Armed Forces Institute of Pathology, the Museum of Hygiene, the National Museum, the Smithsonian Institution, the Botanic Gardens, and the collections of the Department of Agriculture, as well as the collections and services of the different special and governmental libraries located here.

These organizations and institutions all afford opportunities for expanded study in the various areas of undergraduate and graduate medicine and allied sciences to the students and practicing physicians from all states in the Union and from some 40 foreign nations at The George Washington University Medical School.

CLOYD HECK MARVIN, Ph.D., *President*
The George Washington University

INTRODUCTION

The faculty of the School of Medicine of The George Washington University, and the staff of The George Washington University Hospital are honored and pleased by the opportunity to participate in the publication of this special issue of Postgraduate Medicine.

Although all schools of medicine are fundamentally similar, each has its individual qualities and traditions which make it distinctive in certain respects from the others. It is extremely fortunate for medicine that such discernible differences in point of view, in emphasis, and in special interests exist among the medical schools, their faculties and their graduates, for this brings to medicine as a whole a greater scope of creativity than would be possible if all medical schools were cast from an identical mold.

A special issue of Postgraduate Medicine devoted to papers from the various departments of one medical school serves the excellent purpose not only of providing clinically useful material, but also of bringing to readers throughout the country some intimation of the distinctive interests of the particular medical school represented.

Although the presence of a medical school in a community automatically makes that city a medical center, the characteristics of the community itself, including its needs and its resources, undoubtedly have an important influence on the direction of the growth and development of the medical school. The fact

WALTER A. BLOEDORN

that the George Washington University School of Medicine during its 130 years has been located in the nation's capital has undoubtedly affected the school's development. It has brought to the School of Medicine students from every state and territory, and from many foreign countries. It has provided the teaching services of a long series of distinguished workers associated with the armed forces, the U. S. Public Health Service, St. Elizabeth's Hospital, veterans hospitals, and various other major medical and scientific establishments of the federal government. It furthermore has made available for teaching the clinical facilities of many of these organizations, supplementing the nonfederal and civilian clinical facilities present in the District of Columbia, including the new University Hospital, the new University Cancer Clinic, Children's Hospital, and D. C. General Hospital. The truly cosmopolitan population of Washington provides a sampling of many diseases which might not otherwise be seen in this particular geographic location.

The George Washington University School of Medicine has made every effort to keep pace with the emergence of Washington as one of the world's great medical centers, and in the future, as in the past, will strive not only to keep pace, but to provide a share of leadership in the growth of Washington's medical community.

The faculty of The George Washington University School of Medicine wishes to take this opportunity to extend to readers of POSTGRADUATE MEDICINE an invitation to visit the School, the University Hospital, and its other facilities at any opportunity that may arise.

WALTER A. BLOEDORN, M.D., *Dean*
The George Washington University
School of Medicine

The Management of Anticoagulant Therapy by a Simple Blood "Prothrombin" Test

BENJAMIN MANCHESTER*

George Washington University School of Medicine, Washington, D. C.

BENJAMIN MANCHESTER

CURRENTLY available anticoagulants depend for their antithrombotic effect on the hypoprothrombinemic activity. Frequent blood prothrombin determinations must be made in order to regulate dosage and to assure safe, effective blood levels. The tests that are currently employed for blood prothrombin determinations require trained technical personnel and special facilities. Often the initiation of anticoagulant therapy requires hospitalization. The added cost and inconvenience and the hazards of bleeding have served to deter many physicians from using anticoagulants in prevention and treatment of thrombo-embolic disease.

*Department of Medicine, George Washington University School of Medicine; George Washington University Medical Service, District of Columbia General Hospital, Washington, D. C.

The purpose of this report is to present the experience and management of anticoagulant therapy by means of a simple blood "prothrombin" test. The method has been employed since 1945 in more than 1100 individuals. It has been possible, with this test, to continue long-term anticoagulant therapy in the office and at the bedside. It has eliminated the additional expense of hospitalization. Anticoagulants were thus made available to many patients without resorting to elaborate laboratory facilities for the more conventional blood prothrombin tests.

Material and Method

Of a total of 938 patients with thromboembolic diseases, 604 received anticoagulant therapy; 334 patients served as alternate controls in the study of myocardial infarction[1] and in the series of cases of chronic congestive heart-failure.[2] The distribution of the material is shown in table 1.

Of the 604 patients who received anticoagulants, 140 (23 per cent) received heparin and

TABLE 1

DISTRIBUTION OF CLINICAL MATERIAL

	NUMBER OF CASES	
	Anticoagulant group	*Control group*
Myocardial infarction	150	150
Chronic congestive heart-failure	184	184
Pulmonary embolism	48	0
Thrombophlebitis of the legs	64	0
Postoperative prophylaxis in patients over 60 years of age	66	0
Cerebral thrombosis	64	0
Arterial embolism	21	0
Mesenteric thrombosis	2	0
Central retinal vein thrombosis	5	0
	604	334

DICUMAROL[30]. The remainder received Dicumarol alone. The initial dose of Dicumarol was 200 to 300 mg. Thereafter, 100 mg. was given daily until the prothrombin level was in the therapeutic range. For those who received heparin, a prothrombin test was made three to four hours after the last dose or when the clotting time was normal. Prothrombin determinations were performed daily during the first 30 days, then weekly for six or more weeks.

Technic

The bedside method employs whole capillary blood. Two hemoglobin pipets, a concave slide, a stop watch, physiologic saline solution and thromboplastin are the required materials. The thromboplastin is prepared from acetone-desiccated rabbit brain as recommended by Quick.[3] To 4 cc. of physiologic saline solution, 0.15 gm. of dried powdered rabbit brain is added. The mixture is then incubated for 20 minutes at 40° C.

Twenty cubic millimeters of thromboplastin warmed to 37° C. is placed on a warm, dry slide, and an equal amount of free-flowing capillary blood, obtained by a simple needle puncture of a finger, is added. The slide is tilted gently back and forth until a coagulum is formed. The time in seconds is the "prothrombin" time. The "total clotting time" for capillary blood is 15 to 18 seconds, with a standard deviation of 2.5 seconds. A normal blood prothrombin time is always taken on a control before it is determined on a patient. The therapeutic level is maintained at twice the normal (36 to 40 seconds). When the prothrombin time is expressed as a percentage of the normal the therapeutic level was maintained between 40 and 60 per cent. The equation for this determination is:

$$\text{Prothrombin index} = \frac{\text{normal prothrombin time}}{\text{patient's prothrombin time}} \times 100.$$

A comparison of this method with the Quick and Link-Shapiro (12.5 per cent plasma dilution) blood prothrombin tests is shown in table 2. It compares favorably with the Link-Shapiro method. The values expressed in per cent in the Quick blood prothrombin test are based on a hyperbolic dilution curve. When the bedside prothrombin test, expressed in per cent, is 60 to 40, this corresponds to Quick prothrombin time expressed as 30 to 10 per cent, respectively. The bedside prothrombin test is discussed in greater detail in another report to be published.[4]

Results

The 300 patients with myocardial infarction, of whom 150 served as controls, were classified according to the criteria of Russek and Zohman[5] as good-risk and poor-risk subjects. Those who had previous myocardial infarction, angina pectoris, intractable pain, severe shock, cardiomegaly, congestive heart-failure, auricular fibrillation or other serious arrhythmia, previous pulmonary embolism, or other states predisposing to thrombosis were placed in the poor-risk category. Patients without the above signs or symptoms were classified as good risks. The grouping was based on the clinical examination excluding the electrocardiographic and other laboratory studies.

The total mortality in the control group was 42, or 28 per cent, and in the anticoagulant group, 18, or 12 per cent (table 3). Clinical thrombo-embolic phenomena occurred in 26 (17.3 per cent) and nine (6 per cent) of cases in the control and anticoagulant groups, respectively.

Among the 47 good risks in the control

TABLE 2—*A Comparison of the Bedside Prothrombin Test with the Quick, and the Link-Shapiro Methods**

| Days of treatment | Patient | | |

TABLE 3

SUMMARY OF 300 CASES OF CORONARY OCCLUSION WITH MYOCARDIAL INFARCTION (PATIENTS SURVIVING FIRST DAY OF ILLNESS)*

	ANTICOAGULANT GROUP		CONTROL GROUP	
	Number	*Per Cent*	*Number*	*Per Cent*
Total cases	150		150	
Sex distribution				
Males	126	84	121	80.6
Females	24	16	29	19.4
Previous infarct	42	28	34	23
Good risks	33	22	47	31
Poor risks	117	78	103	69
Heparin and Dicumarol	108	72		
Dicumarol alone	42	28		
Thrombo-embolic complications	9	6	26	17.3
Number of deaths	18	12	42	28

*Average age of patients: anticoagulant group, 58.5 years; control group, 61 years.

group, there were six deaths (12.8 per cent). Among the 33 good risks in the anticoagulant group there were three deaths (9.1 per cent).

Thrombo-embolism occurred in two of the good risks, or 4.2 per cent. Embolism was fatal in both cases. Death occurred 14 and 18 days, respectively, after the onset of illness, during otherwise uneventful convalescence. In the anticoagulant group, thrombo-embolism also occurred in two cases, but the patients recovered (table 4).

The mortality in the 103 poor risks in the control group was 36 (35 per cent), whereas in the anticoagulant group of 117 there were 15 deaths (12.8 per cent). Thrombo-embolic complications in these poor risks showed a corresponding contrast. They occurred in 24 (23.3 per cent) of the control group and in only seven (5.9 per cent) of the anticoagulant group. Death due to pulmonary embolism occurred 12 times among poor risks in the control group and once in the anticoagulant group. Pulmonary embolism in the remaining cases of both groups complicated by thrombo-embolism was the precipitating cause of severe congestive heart-failure.

In poor risks with two or more myocardial infarctions treated with Dicumarol the prognosis was better than in the comparable control patients. Among 42 such patients who received anticoagulant therapy, nine died (21.3 per cent) (table 5). Embolization oc-

TABLE 4

MORTALITY RATE AND INCIDENCE OF THROMBO-EMBOLIC COMPLICATIONS IN 300 PATIENTS WITH MYOCARDIAL INFARCTION

	TOTAL CASES		DEATHS		EMBOLISM	
	Control	*Anticoagulant*	*Control*	*Anticoagulant*	*Control*	*Anticoagulant*
Good risks	47	33	6 (12.8%)	3 (9.1%)	2* (4.2%)	2† (6.0%)
Poor risks	103	117	36 (35%)	15 (12.8%)	24 (23.3%)	7 (5.9%)
TOTAL	150	150	42 (28%)	18 (12%)	26 (17.3%)	9 (6.0%)

*Fatal.
†Patients recovered.

TABLE 5

MORTALITY RATE AND INCIDENCE OF THROMBO-EMBOLIC COMPLICATIONS IN PATIENTS WITH PREVIOUS INFARCTIONS

	TOTAL CASES	DEATHS		EMBOLISM	
		Number	*Per Cent*	*Number*	*Per Cent*
Anticoagulant group	42	9	21.3	4	9.5
Control group	36	21	58.3	14	38.8

curred in four cases, or 9.5 per cent. In the control group of 36 subjects there were 21 fatalities, or 58.3 per cent, and embolism occurred in 14 cases, or 38.8 per cent.

The causes of death in the control group of 150 were as follows: In 12 cases, death followed pulmonary embolism; two patients died of ruptured hearts 14 and 20 days, respectively, after onset of the illness; 20 died of congestive heart-failure; four died of extension of the myocardial infarct, and in four cases the cause of death was undetermined. Of 18 fatalities in the entire anticoagulant series of 150 cases, one was due to pulmonary embolism, nine were from congestive heart-failure, three were sudden, unexplained deaths, one was due to respiratory depression following intravenous morphine, and four to unknown causes.

The effectiveness of anticoagulant prophylaxis in congestive heart-failure as reflected in the reduced incidence of thrombo-embolism and mortality is shown in the 184 treated patients as compared with the control group. The mortality rate in the control series was 15.7 per cent (29 deaths), and in the anticoagulant group it was 6.5 per cent (12 deaths). Thrombo-embolism occurred in 10 per cent of the control group and only 1 per cent of the anticoagulant group.

In the 48 patients with pulmonary embolism, the mortality rate was 10.4 per cent (five deaths). Far-advanced disease was present in this group and complicated by either underlying heart disease or extensive surgery.

The role of anticoagulants or their effectiveness in cerebral thrombosis is difficult to evaluate. While recovery seemed to be greater, the series is too small to be significant.

In the postoperative patients over the age of 60 years who received anticoagulant therapy 72 to 96 hours after surgery, not a single instance of pulmonary embolism or peripheral thrombosis was noted.

The remainder of the group who received anticoagulants received Dicumarol alone or with heparin, in addition to vasodilators, sympathicolytic drugs and surgery. Their effectiveness cannot be evaluated. However, in not a single instance in this group of 92 patients did anticoagulant therapy deter recovery or delay progress and improvement.

Complications

The complications encountered were limited to hemorrhagic manifestations due to the hypoprothrombinemia. Twenty-two patients manifested bleeding as a complication. If one excludes epistaxis, ecchymoses and bleeding from the gums, the actual incidence of hemorrhagic complications was only 1 per cent. Withdrawal of the anticoagulant employed and prompt administration of vitamin K_1 oxide (MEPHYTON®, 50 mg., intravenously) produced a return of the blood prothrombin level within 24 to 36 hours. More recently, the single administration of vitamin K_1 orally, in doses of 100 mg., produced a return of the blood prothrombin level to normal within 24 hours. The administration of vitamin K_1, 5 mg. every six hours, produced a similar return of the blood prothrombin level to normal. In only one instance, our very first hemorrhagic complication, was it necessary to hospitalize the patient and resort to blood transfusions. In the remainder, vitamin K_1 orally or intravenously was adequate to restore the blood prothrombin level to normal.

Discussion

The greatest deterrent to the use of Dicumarol therapy has been the unavailability of a simple, accurate and inexpensive method for measuring blood prothrombin activity. Methods currently employed require trained technical personnel and laboratory facilities. This report is unique in one respect: Dicumarol has been given to patients for the prevention and treatment of thrombo-embolic disease in the home as well as in the hospital. Effective antithrombotic levels as measured by a simple blood prothrombin test were maintained without the increased hazard of bleeding.

Whole blood for performing a blood prothrombin test has been employed by many investigators in the past. A similar method employing capillary blood was first described by Quick in 1939.[6] Tocantins[7] has employed whole venous blood for the Ziffern-Smith prothrombin test in his routine control of anticoagulant therapy. Bruzelius[8] in Sweden has used a similar micromethod for Dicumarol therapy. Several modifications of a similar type of prothrombin test have been reported.[9-11] So far as is known, this report is the first to deal with a large series of patients with thrombo-embolic disease in which Dicumarol dosage has been controlled by such a simple blood prothrombin test.

Through the prerequisite use of a control normal blood prothrombin test, the physician is aware of the degree of activity of the thromboplastin employed. This control test also supplies him with a reference to compare the accelerated clotting activity of the patient with the normal. This precaution has served to detect a loss of thromboplastin activity when it otherwise would have been overlooked. It also made possible the detection of 14 cases of anicteric hepatitis among individuals who served as controls.

A comparison of this bedside "prothrombin" test with current one stage procedures shows it to have much in common with the latter. The term "prothrombin test" for such methods is a misnomer. Both measure more than prothrombin activity. The one stage prothrombin test measures prothrombin, fibrinogen and accelerator factors.[12] The prothrombin time, therefore, is an accelerated "clotting test" and reflects more than the prothrombin concentration.

The present method is not without pitfalls. The accuracy and sensitivity of this test were dependent on an active and reliable source of thromboplastin. While normal plasma yielded the same prothrombin time with different types of thromboplastin, Dicumarol plasma behaved differently with various types. The results reported herein can be reproduced only if desiccated acetone-dehydrated rabbit brain is used as the source of thromboplastin. The thromboplastin activity may vary with the age, temperature and amount employed. A control prothrombin time must always be determined first on a normal subject.

The described test has proved to be a valuable practical guide to Dicumarol therapy for the prevention of thrombo-embolic complications. At the same time it was possible to detect hypoprothrombinemia and to prevent hemorrhagic complications. The usefulness of the simple blood prothrombin test for the control of Dicumarol and other oral anticoagulants is reflected in the therapeutic efficacy and safety noted in this series. The results compare favorably with the reports of other investigators using other prothrombin tests.

The collective statistics from the proponents of anticoagulant therapy have been critically probed for defects and inaccuracies. Those who challenge the value of anticoagulant therapy emphasize the comparable low incidence of mortality in good risks not treated with anticoagulants. The occasional thrombo-embolic complication would have little influence on the over-all mortality rate and hence would justify their view. However rare, this complication did occur and proved fatal to two patients in our control group. While the increased mortality from such a complication was only 4.2 per cent (hardly significant statistically), the unpredictability of such a complication in a good risk increased the responsibility of avoiding a preventable fatality from thrombo-embolism. To a family, the survival of such a patient assumes greater importance than any significant statistical figure. These

observations are in agreement with Wright's[13] earlier admonitions.

The use of anticoagulants has likewise proved to be of value in preventing thromboembolic complications in severe congestive heart-failure. The mortality rate was 15.7 per cent for controls and 6.5 per cent in the anticoagulant group. The incidence of thromboembolism was 10 per cent as against 1 per cent in the control and anticoagulant groups, respectively. These results are in accord with reports by Anderson and Hull,[14,15] Harvey and Finch,[16] and Levinson and Griffith.[17]

Reluctance in using anticoagulant therapy stems from the hazard and fear of hemorrhage which is always present whenever such therapy is employed. Technical difficulties increase this potential. Hence, a reluctance to employ such a regimen is understandable. Frequent prothrombin determinations, made possible by this simple test, elicited levels of hypoprothrombinemia before hemorrhagic complications could develop. The ease with which this test can be performed makes serious hypoprothrombinemia less likely, or at least renders its recognition readily and conveniently. The incidence of hemorrhagic complications in this series was low and compares well with previous reports. Withdrawal of the anticoagulant and administration of vitamin K_1 oxide (Mephyton), 50 mg. intravenously, or vitamin K_1 orally in doses of 100 mg. daily, or 5 mg. every six hours, were always effective in stopping bleeding or in preventing it. It was unnecessary to hospitalize patients or to administer blood. Bleeding ceased within two days. There were no deaths from this cause.

Summary

Administration of anticoagulants at home and in the hospital in cases of acute myocardial infarction, congestive heart-failure, pulmonary embolism and other thrombo-embolic diseases was made possible by a simple capillary blood "prothrombin" test. The management of 604 patients is presented.

The mortality rate was lower, and the thrombo-embolic complications were fewer, in the group receiving anticoagulants as compared with the control group. Except for receiving the specific anticoagulant alone or with heparin, both groups followed the same regimen and received the same medication.

The results indicate that this blood "prothrombin" test is a practical bedside, office or hospital procedure. It has eliminated the need for hospitalization and has made therapy available at home, in the office and in communities where trained technical personnel or special equipment is unavailable. The method is simple, accurate, reproducible and practical. It is inexpensive; it eliminates venipuncture and hence makes blood "prothrombin" determinations feasible in infancy. The hazards of bleeding were minimal.

It is hoped that others will find this method useful in the management of anticoagulant therapy.

REFERENCES

1. Manchester, B. and Rabkin, B.: Control of Dicumarol therapy in myocardial infarction. Circulation 10:691, 1954.
2. Manchester, B.: The value of anticoagulant therapy in chronic heart failure. (To be published.)
3. Quick, A. J.: The Hemorrhagic Diseases. Springfield, Illinois, Charles C Thomas, 1942.
4. Manchester, B.: A simple blood prothrombin test for the control of Dicumarol therapy. M. Ann. District of Columbia (to be published).
5. Russek, H. I. and Zohman, B. L.: Present status of anticoagulant therapy in acute myocardial infarction. Quart. Rev. Med. 9:1, 1952.
6. Quick, A. J.: Determination of prothrombin. Proc. Soc. Exper. Biol. & Med. 42:788, 1939.
7. Tocantins, L. M.: Personal communication to the author. 1949.
8. Bruzelius, S.: Dicoumarin in clinical use; studies on its prophylactic and therapeutic value in treatment of thrombo-embolism. Acta chir. Scandinav. 92:1, 1945.
9. Kato, K.: Micro-prothrombin test with capillary whole blood. Am. J. Clin. Path. 10:147, 1940.
10. Abramson, D. J. and Weinstein, J. J.: A rapid bedside microprothrombin test. Am. J. Clin. Path. 12:1, 1942.
11. Innes, J. and Davidson, L. S. P.: A simple method of estimating prothrombin in capillary blood. Brit. M. J. 1:621, 1941.
12. Alexander, B., deVries, A. and Goldstein, R.: Prothrombin: A critique of methods for its determination and their clinical significance. New England J. Med. 240:403, 1949.
13. Wright, I. S.: Experiences with Dicumarol (3,3′ methylene-bis [4-hydroxycoumarin]) in the treatment of coronary thrombosis with myocardial infarction. Am. Heart J. 32:20, 1946.
14. Anderson, G. M. and Hull, E.: The use of Dicumarol as an adjunct to the treatment of congestive heart failure; results in a controlled series of sixty-one cases. South. M. J. 41:365, 1948.
15. ——: The effect of Dicumarol upon the mortality and the incidence of thromboembolic complications in congestive heart failure. Am. Heart J. 39:697, 1950.
16. Harvey, W. P. and Finch, C. A.: Dicumarol prophylaxis of thromboembolic disease in congestive heart failure. New England J. Med. 242:208, 1950.
17. Levinson, D. C. and Griffith, G. C.: Evaluation of anticoagulant therapy in congestive heart failure. Circulation 4:416, 1951.

Pectus Excavatum

BRIAN BLADES, OWEN GWATHMEY AND PAUL C. ADKINS*

George Washington University School of Medicine, Washington, D. C.

BRIAN BLADES

PECTUS excavatum is a depression of the lower portion of the sternum and of the adjacent costal cartilages. Other synonyms for this condition are funnel chest, trichterbrust, koilosternia, chonechondrosternon and sunken chest;[1] however, pectus excavatum is the most widely used term for this deformity.

Characteristically, the condition becomes more marked as growth progresses. The sternal depression may be a psychologic handicap or, if severe, may cause cardiorespiratory difficulty. Surgical correction is the treatment of choice. The operative risk is small, and the results are excellent.

In 1596 Bauhinus[2] described this lesion accurately and stated that the pull of the diaphragm was the causative factor. Numerous articles on this deformity appeared in the European literature during the nineteenth century, and many theories were advanced concerning its etiology. During this period the familial tendency of pectus excavatum was well documented.

Surgical intervention for the relief of pectus excavatum was first attempted by Meyer[3] in 1911. Although the result was not satisfactory, it led the way to more successful procedures by Sauerbruch,[4] Lexer[5] and Alexander.[6] In general, however, the operation was reserved for only the most severe deformities. The majority of the patients were treated by postural training and breathing exercises.

Within the past 15 years a great deal has been learned about the pathogenesis and treatment of pectus excavatum. Contributions of Brown,[7] Ochsner and DeBakey,[8] Lester,[9] Ravitch,[10] Sweet[11] and others have been outstanding. Improved anesthesia technics, blood transfusion and other advances in the field of thoracic surgery during the past decades have also made surgical intervention more feasible.

Pectus excavatum is not a common deformity. Ochsner and DeBakey,[8] reviewing the literature, found that the incidence was

*Department of Surgery, George Washington University School of Medicine, Washington, D. C.

0.059 per cent of the population. This was an average taken from several series reported and represented examinations on a total of 46,705 persons. This figure represents the incidence of true pectus excavatum and excludes other deformities of the sternum which could be ascribed to rickets, trauma or other causes. Ochsner and DeBakey also stated that of the reported cases in the literature, males were found to predominate in a ratio of approximately four to one.

OWEN GWATHMEY

PAUL C. ADKINS

Etiology

Many factors have been mentioned as possible etiologic agents in pectus excavatum. Among these are intra-uterine pressures, rickets, obstruction of the upper respiratory tract, heredity, neurologic lesions and syphilis.[1,7,8]

Heredity appears to be the only etiologic agent with basis for fact, since the condition is congenital and definite familial tendency has been demonstrated. Some observers feel that laryngeal obstruction in infancy plays an important part in its development. Association of rickets has been disproved, since very few patients have any other demonstrable rachitic deformities. Intra-uterine pressures as a cause have been termed by Brown[7] as "fantastic." Syphilis and neurologic lesions have not been shown to have any consistent relationship with this deformity.

Pathologic Anatomy

The deformity usually begins at the junction of the manubrium and the body of the sternum (gladiolus). The depression becomes more marked inferiorly at or near the junction of the body of the sternum and the xiphoid process. The sternum may be so depressed that it reaches the vertebral bodies in severe cases. Frequently an axis deviation may be present so that the sternum is deviated toward the paravertebral gutter on one side. Abnormalities in size and position of the xiphoid are often noted. The costal cartilages adjacent to the depressed portion of the sternum are directed obliquely inward, causing an angulation at the costochondral junction. This angle forms the rim of the funnel deformity.

Brown[7] has emphasized the importance of the central tendon of the diaphragm in the production of pectus excavatum. The central tendon is attached to the undersurface of the lower sternum and xiphoid by the substernal ligament. It normally flattens out during inspiration, increasing the volume of the thoracic cage. If the tendon is short, it attains maximum flattening early in inspiration. Consequently, any further contraction of the diaphragm increases the pull on the substernal ligament, and results in a dorsal displacement of the xiphoid and lower sternum. This mechanism probably plays the major role in the sternal deformity in the first year of life. In older children and adults, however, irreversible changes have occurred in the bony thorax, so that other factors must also be considered in undertaking the correction of the deformity.

Diminution in the anteroposterior diameter of the mediastinum results from depression of the sternum below the level of the anterior chest wall. This may result either in compression of the heart between the sternum and vertebral column (figure 1a and b) or, more commonly, in displacement of the heart and other mediastinal structures to one side. In most instances the heart is displaced to the left (figure 2a and b) and may rotate on its long axis. In either case, cardiac symptoms may result from compression or severe displacement. Likewise, respiratory symptoms may result from mediastinal displacement or from limitation of respiratory excursions as a result of the deformity. Patients with a severe pectus excavatum are more prone to chronic respiratory infections, since an effectual cough is often difficult.[9]

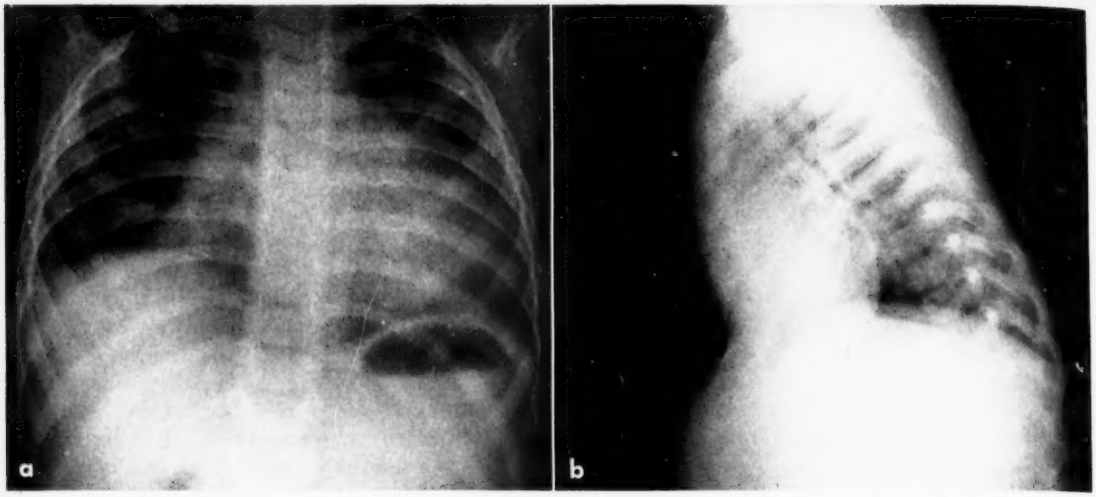


FIGURE 1a and b. Chest films showing pectus excavatum with compression of the heart between the mediastinum and vertebrae.

In addition to the changes brought about by the chest wall deformity, certain other characteristics are present in patients with pectus excavatum. The patient is usually stoop-shouldered, with an increase of the dorsal curve of the spine. The abdomen is usually more protuberant, particularly in young children.

Clinical Manifestations

In the majority of instances the presence of a pectus excavatum is recognized by the pediatrician within the first few months of life. In others, however, the condition may go unrecognized until the child is of school age, or even later. Uncorrected, the deformity almost invariably will progress until full growth is attained, and possibly even after that.

The degree of depression of the sternum varies greatly. The majority of patients are free of symptoms and the only clinical manifestation is the cosmetic defect of the chest wall. With marked depression, however, some symptoms are usually present. Evidence of cardiorespiratory embarrassment may occur

FIGURE 2a. Film of pectus excavatum showing mediastinum shifted to left. b. Film of pectus excavatum showing scoliosis and mediastinum shifted to the left.

as a result of the mediastinal compression or displacement. The most common cardiac symptoms are exertional dyspnea, palpitation and precordial discomfort. In cases of very severe deformities, heart-failure, cyanosis and auricular fibrillation have been reported.[12] Respiratory symptoms of exertional dyspnea and chronic cough are frequent. Chronic respiratory infections may be present, and failure to gain weight as a result of repeated infections is not uncommon. The vital capacity is frequently low and may be only half the normal value.[8]

The degree of incapacity may not be apparent from superficial questioning. A careful history of the patient's activities and a comparison with those of other children or members of the family may reveal considerable limitations which have not really been appreciated.

Complaints of a psychologic nature may arise as a result of the cosmetic deformity. It may cause undue embarrassment particularly during adolescence or young adulthood, especially in females. They may shun beaches and other public gatherings where their deformity may be apparent. In these persons the psychologic effects of a sunken chest may be far-reaching and disastrous if the defect is not corrected.

Treatment

Patients with minimal deformity require only postural training to correct the dorsal curvature of the spine and slumping of the shoulders. The more marked defects, however, need surgical intervention. Since pectus excavatum is progressive in nature, the condition should be corrected before cardiorespiratory symptoms occur. In the early stages of the abnormality the operation is less formidable and the cosmetic results are better.

Opinions concerning the details of operation for pectus excavatum differ markedly. However, two principles must be observed: (1) the division of the substernal ligament and (2) the resection of costal cartilages and wedge osteotomy of the sternum. The numbers and extent of cartilage resection will vary with the individual case.

Division of the substernal ligament alone gives a better result if accomplished in infants under one year of age. This is done by making a small incision over the xiphoid, excising it and sectioning the attachments of the substernal ligament to the sternum and adjacent costal arch. The retraction of the sternum during inspiration is alleviated, and the depression is not as apparent in most instances. Correction may not be complete, but resiliency of the chest wall, growth of the infant and postural training will further improve this deformity in most cases. The advantages of this operation are: (1) It may avoid a more radical procedure later, (2) the operation is short and relatively atraumatic and (3) it may prevent the development of cardiorespiratory symptoms and psychologic trauma in later life.

A more radical operation is necessary to correct the depression once the resiliency of the chest wall is lost, or if the deformity is marked. If the operation is performed before five years of age, a better functional and cosmetic result may be expected. The procedure consists of a midline longitudinal incision extending from the manubriosternal junction to approximately 2 cm. below the xiphoid. The xiphoid is excised, and the substernal ligament attachments to the sternum and costal arch are sectioned. The ventral space is entered, and the undersurface of the sternum is freed from the mediastinal structures. The costal cartilages adjacent to the depressed segment of the sternum are exposed by splitting the pectoralis muscle. A wedged segment is excised from each of these cartilages. A transverse wedge osteotomy across the outer table of the sternum is done at the upper level of the depression. A greenstick fracture of the sternum is then accomplished. The depressed segment is then mobile. The pull of the pectoralis muscles usually will keep the segment elevated if the depression is not too severe.

If the deformity is not satisfactorily corrected, a rib strut may be used. The strut is a homologous rib graft preserved in a freezer under sterile conditions. This is anchored to the fifth costochondral junction on each side with chromic catgut. The use of a strut gives

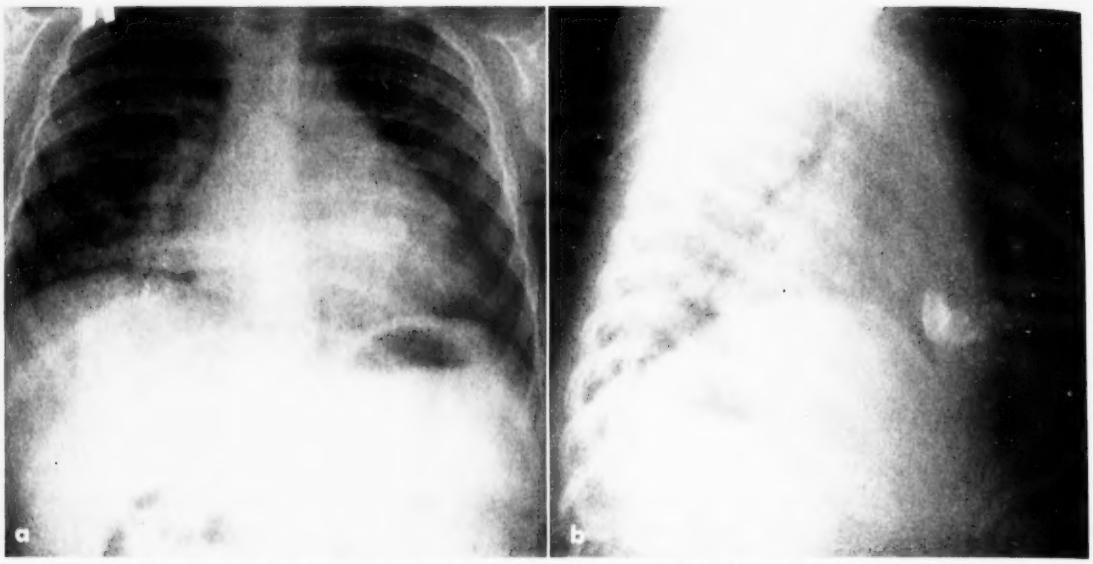


FIGURE 3a and b. Same patient as in figure 1, after elevation of sternum and placement of a rib strut.

an excellent cosmetic result and prevents paradoxical respiration (figure 3a and b).

In more severe cases and especially in adults, a longitudinal midline wedge osteotomy of the sternum may be necessary to correct the concavity. More radical excision of the costal cartilages is usually necessary and varies with the individual deformity. A rib strut is again employed to maintain elevation of the sternum.

Some surgeons prefer to employ traction[13,14] to hold the sternum in an overcorrected position. This is done by passing a wire through the sternum and attaching it to a bridge on the anterior chest wall or incorporating it into a plaster jacket. We feel, however, that this is not necessary since the use of a rib strut will accomplish the same end results without the disadvantage of the traction mechanism.

The substernal space is drained in all cases. Water-seal drainage is established on the appropriate side if the pleural cavity has been entered.

Postoperative care does not require special apparatus for protection of the chest wall. Those cases in which rib struts are not used are benefited by the use of a posterior figure-of-8 plaster bandage to hold the shoulders back. This should be maintained for four to six weeks.

Summary

1. Pectus excavatum is amenable to surgical correction.

2. The etiology, pathologic anatomy and clinical manifestations have been discussed.

3. Operation is advocated to prevent or correct cardiorespiratory difficulty or social inhibitions as a result of the deformity.

REFERENCES

1. LESTER, C. W.: Funnel chest: Its cause, effects and treatment. J. Pediat. 37:224, 1950.
2. RAUHINUS, J.: Quoted by BROWN, A. L.[7]
3. MEYER, L.: Cited by OCHSNER, A. and DEBAKEY, M.[8]
4. SAUERBRUCH, F.: Cited by OCHSNER, A. and DEBAKEY, M.[8]
5. LEXER: Cited by OCHSNER, A. and DEBAKEY, M.[8]
6. ALEXANDER, J.: Traumatic pectus excavatum. Ann. Surg. 93:189, 1931.
7. BROWN, A. L.: Pectus excavatum (funnel chest). J. Thoracic Surg. 9:164, 1939.
8. OCHSNER, A. and DEBAKEY, M.: Chone-chondrosternon. J. Thoracic Surg. 8:469, 1938.
9. LESTER, C. W.: The surgical treatment of funnel chest. Ann. Surg. 123:1003, 1946.
10. RAVITCH, M. M.: The operative treatment of pectus excavatum. Ann. Surg. 129:429, 1949.
11. SWEET, R. H.: Pectus excavatum. Ann. Surg. 119:922, 1944.
12. RAVITCH, M. M.: Pectus excavatum and heart failure. Surgery 30:178, 1951.
13. LESTER, C. W.: Funnel chest and allied deformities of the thoracic cage. J. Thoracic Surg. 19:507, 1950.
14. GROSS, R. E.: Surgery of Infancy and Childhood. Philadelphia, W. B. Saunders Company, 1953, chapter 57 (pp. 757-760).

Brucellosis and Heart Disease

I. THE SHAKY FOUNDATIONS OF "RHEUMATIC" HEART DISEASE

THOMAS M. PEERY*

George Washington University School of Medicine, Washington, D. C.

Is rheumatic fever the only febrile illness which may cause chronic valvular heart disease? Is "rheumatic fever" a disease entity? These questions have become important as a result of certain studies strongly suggesting that brucellosis may cause chronic valvular heart disease. To answer them we must consider critically the present state of our knowledge of rheumatic fever.

THOMAS M. PEERY

The modern concept of rheumatic fever is based on a series of clinical, bacteriologic, immunologic and pathologic observations, some of which can be traced far back in medical history. How do these observations stand up when considered in the light of proved facts?

*Department of Pathology, George Washington University School of Medicine, Washington, D. C.

The Clinical Syndrome of Rheumatic Fever

Historically, the first step in the identification of rheumatic fever as we understand it today was taken by Baillou[1] (1538-1616), who distinguished "acute rheumatism" from the chronic disorders of the extremities causing pain, aching or stiffness. Haygarth[2] noted in 1805 that fever occurred in certain cases of acute rheumatism, and proposed the name "rheumatick fever" for this group. Subsequently, certain specific acute febrile diseases manifested chiefly by pains in the extremities have been identified: osteomyelitis, gonorrheal and other forms of septic arthritis, etc. These were split off from the remainder for which no cause could be found.

Meanwhile it had been noted by Wells[3] in 1812 that rheumatism tended to affect the heart. Bouillaud[4] pointed out the essentially valvular nature of this involvement.

The modern concept of rheumatic fever has formed at a point where these two lines of

thought intersect, i.e., where acute rheumatism of unknown cause coincides with valvular heart disease. At this intersection has been built the clinical syndrome of rheumatic fever.

As the syndrome has taken form, many have come to believe that rheumatic fever is a specific entity rather than a syndrome, and that chronic valvular heart disease is essentially a sequela of rheumatic fever. But these two beliefs are by no means proved.

There is no real clinical evidence that rheumatic fever is the only febrile illness causing chronic valvular heart disease. In this connection, brucellosis may be considered briefly.

The similarities between rheumatic fever and brucellosis, first described by Hughes,[5] can best be noted by listing the classic features of rheumatic fever and noting whether or not they occur in brucellosis. Jones[6] has described five major manifestations of rheumatic fever and seven minor ones, and has stated that if any two of the major manifestations or any one major manifestation and any two minor manifestations occur in a given case, the diagnosis of rheumatic fever is reasonably certain.

All 12 of these manifestations of the clinical syndrome of rheumatic fever, with the possible exception of chorea, occur commonly in brucellosis. Almost every case of brucellosis will show two of the major manifestations, arthralgia and recurrences. The five major manifestations of rheumatic fever as given by Jones[6] are listed below, together with a discussion of their occurrence in brucellosis.

1. Carditis—Although it is not generally known, cardiac involvement in some degree is not rare in brucellosis. It was described by Veale[7] in 1879 and recognized by Hughes[5] in 1897. It was the subject of a special communication by Bassett-Smith[8] in 1906. Each of these authors commented on the serious nature of the cardiac complications but noted that they need not prove fatal. Endocarditis is the chief cause of death in fatal brucellosis.[9] Chronic valvular heart disease may be a sequela of nonfatal brucellosis.[10] Electrocardiographic changes are almost constant in active brucellosis.[11]

2. Arthralgia—Pain in the joints, with or without redness and swelling, is an integral part of brucellosis.[5,12-14] The arthritis is usually migratory and is ordinarily followed by complete resolution.

3. Chorea—Evidence of encephalitis has been noted frequently during the course of brucellosis,[15-20] but the resemblance to Sydenham's chorea is apparently not striking.

4. Subcutaneous nodules—Such nodules have been noted repeatedly during the course of brucellosis.[7,21,22]

5. Recurrences—Brucellosis is seldom considered until two or more recurrences have suggested the possibility of this diagnosis.

The seven minor manifestations of rheumatic fever as listed by Jones[6] are given below and their occurrence in brucellosis noted.

1. Fever—This is a feature of almost every case of brucellosis.

2. Abdominal pain—Simpson[23] in particular noted the importance of this symptom in brucellosis and stated that appendectomy was performed in four of the 90 cases of undulant fever in his series. Many others have referred to abdominal pain as a feature in their cases.

3. Precordial pain—Pain over the precordium has been a conspicuous symptom in both fatal and nonfatal cases of brucellosis, especially in those patients showing carditis.[9-11]

4. Rashes—Dalrymple-Champneys[24] noted various rashes in about 10 per cent of his cases. Veale[7] and Harris[21] described erythema nodosum in some of their patients. Others have observed purpuric rashes.[25-27]

5. Epistaxis—Nosebleeds may occur in children[28] and adults.[7,16,29,30]

6. Pulmonary findings—X-ray evidence of parenchymal infiltration of the lungs has been noted in brucellosis.[29,31,32] Simple pleurisy[7,32,33] and empyema[34] have also occurred. Hemoptysis has been observed in several cases.[5,25,35]

7. Laboratory findings—Mild microcytic anemia, elevated leukocyte count and increased sedimentation rate are the most important laboratory findings in rheumatic fever, according to Jones.[6] These may also occur in brucellosis[24,36] although a normal or reduced leukocyte count is more typical.[36]

Thus, all the major manifestations of the

rheumatic fever syndrome (with the possible exception of chorea) and all the minor manifestations may occur in brucellosis. On the basis of clinical symptoms and signs there is no possibility of differentiating these two diseases with certainty.

Bacteriologic and Immunologic Features of Rheumatic Fever

Rheumatic fever cannot be differentiated from other diseases on the basis of bacteriologic or serologic tests. As noted by Waksman,[37] many different bacteria have been isolated from the throat, blood, joints and heart valves in cases of rheumatic fever, but these organisms are not different from those which may be obtained in many other respiratory diseases. Streptococci, particularly those of the group A strain, have been incriminated, but the data are so complex[38] that the evidence is inconclusive. Increased antistreptolysin values occur after hemolytic streptococcal infections without regard to whether or not rheumatic fever develops; this test is therefore not diagnostic.[6] Waksman[37] is of the opinion that streptococci are "nonspecific provocatives" of rheumatic fever; he notes that malaria, dysentery or trauma may also sometimes provoke an attack of acute rheumatic fever.

It is popular at the moment to consider that rheumatic fever is a manifestation of antigen-antibody interaction. Thus in various conditions there may be a release of antigen, to which the tissues react by the production of antibody. The interaction of antigen and antibody may produce an inflammatory response in certain tissues of the body, including the joints and the heart valves. Without arguing the merits of this concept, it should be noted that such a mechanism is believed to operate in many diseases of different etiology and is by no means distinctive of rheumatic fever. Furthermore, the concept offers no aid to the diagnosis of rheumatic fever.

Pathology of Rheumatic Fever

As Paul[39] has noted, it is the Aschoff body in the myocardium more than any other single factor which has led physicians to believe that rheumatic fever is a disease entity. This lesion has generally been considered as a specific reaction to an unknown but specific etiologic agent.

But even the Aschoff body must be questioned. In the first place it is not always present in fatal cases which have shown the clinical syndrome of rheumatic fever. Clawson[40] has quoted different authors as finding Aschoff nodules in from 32 to 87.5 per cent of fatal cases of rheumatic fever. Secondly, such nodules have been noted under so many different circumstances that one must question their significance in rheumatic fever. Aschoff bodies were found by Hall and Anderson[41] in 29 per cent of a series of 112 grossly normal, "nonrheumatic" hearts. Similar nodules have been observed in typhoid fever, scarlet fever, pneumococcal pneumonia, syphilis, tuberculosis and meningococcal infections.[40] Comparable or perhaps identical lesions have been produced experimentally[37] by the injection of living or dead streptococci, tubercle bacilli, dysentery organisms, foreign serum, egg albumen, sulfadiazine and the animal's own tissues. Myocardial granulomas, in many instances indistinguishable from Aschoff bodies, have been described in many cases of fatal brucellosis (see tables, Peery and Belter[9]).

Some workers, Waksman[37] included, doubt that the lesions produced by experimental means are identical with the Aschoff nodule. But there is probably less difference between the lesions produced by these different methods than there is between the various stages of the naturally occurring Aschoff nodule that have been described and accepted by different workers.

This is the dilemma pertaining to the Aschoff nodule in rheumatic fever: If one requires rigid histologic criteria for its identification, the frequency of acceptable lesions in fatal cases of "rheumatic fever" falls off to an insignificant level; on the other hand, if the histologic criteria are less strict, the nodules are found in such a variety of conditions that they lack specific significance.

It seems reasonable to state that the Aschoff body is probably a nonspecific inflammatory reaction of the connective tissues of the heart

which may be produced by any one of many causes, and that it does not define rheumatic fever as a specific disease. (This is virtually a restatement of Clawson's[40] thesis.)

Discussion

Thus there is no known method of study—clinical, chemical, bacteriologic, serologic or morphologic—applicable either during life or post mortem, that can regularly and positively identify rheumatic fever and separate it from other diseases which it resembles.

But how readily the diagnosis of rheumatic fever is made! Most physicians are completely willing to accept such common past symptoms as recurrent sore throat, fever and joint pains as "positive" history of rheumatic fever. Certainly brucellosis,* and probably many other diseases, cannot be differentiated from rheumatic fever on the basis of such a history.

Is not this attitude unthinking? May it not by its naïveté prevent the recognition of other diseases, such as brucellosis, which may cause chronic valvular heart disease? A brief case report will illustrate this point.

Case Report

A nine year old boy was admitted to a university hospital on January 18, 1938, because of fever, cough, nausea and vomiting of three weeks' duration. A few days after the onset, the left knee became sore and swollen, following which other large joints were affected. On examination the neck veins were pulsating rapidly and the first heart sound was roughened. With bed rest and salicylate therapy the fever and other symptoms subsided in about three weeks. The diagnosis on discharge was acute rheumatic carditis. Joint pain and swelling recurred several times during the spring; he did not return to school during that year.

When 13 years of age, a period of joint pains, fever and pain in the chest occurred requiring continual bed rest for six weeks. During this illness the parents first learned that a heart murmur was present. At age 15 there was a similar recurrence but of less severity.

During the next five years there were occasional episodes of fever, precordial pain and pain in various joints. Dyspnea was noted on climbing one flight of stairs. Any excitement caused breathlessness and throbbing of the heart. The history to this point has been verified from hospital and other records.

At age 24, the patient saw a newspaper account of my studies linking brucellosis to valvular heart disease, and he volunteered to present himself for examination. It was arranged for him to be seen by Dr. John McCallum Evans of the medical department.

He was examined on April 29, 1952. The neck veins were not distended but there was slight cyanosis of the nail beds. The apical impulse was forceful and was maximum 12 to 13 cm. to the left of the midsternal line. A grade 4 blowing diastolic murmur was heard with greatest intensity at the aortic area and was transmitted downward along both borders of the sternum. A grade 2 systolic murmur was also heard at the aortic area and was transmitted upward into the neck. The blood pressure was 160 systolic and 60 to 30 diastolic. On fluoroscopy, dancing calcified conglomerates were noted in the position of the aortic valve cusps. An electrocardiogram showed left ventricular strain and hypertrophy.

The patient gave the following supplemental history, subsequently verified by correspondence with his father. Beginning in 1935, some three years before the patient's first attack of "rheumatic fever," there were numerous abortions among the herd of 40 dairy cows on the farm where the patient and his family lived and worked. Blood samples from the herd were sent to the state university and 10 per cent of those tested were found to be positive for Bang's disease. Because of difficulty in "cleaning up" the herd, the family moved to a new farm and acquired a new dairy herd when the patient was 11 years old. There was evidence of infection in the new herd also. When the boy was 15 years of age, the family moved into the city. From this time on, recurrences of joint pains and fever became less frequent and less severe.

*It is not generally realized that sore throat is common in brucellosis. According to Dalrymple-Champneys,[24] it occurs in one-sixth of the cases and is one of the most important symptoms.

This history of exposure to infected cattle had never been sought by the attending physicians, and a diagnosis of brucellosis had never been considered in this case.

I do not mean to imply that this case of calcific aortic stenosis with regurgitation is necessarily a result of brucellosis. I only wish to point out that the case was considered to be a result of rheumatic fever without thought of any other possible etiologic factor. A blind acceptance of rheumatic fever as the only cause of carditis prevents a thoughtful approach to the problem.

My unpublished data suggest strongly that brucellosis may cause chronic valvular heart disease, particularly calcific aortic stenosis, but probably other types as well. If these observations are confirmed, a new and promising approach to the prevention and treatment of valvular heart disease will be open. But further evaluation of the idea will not be forthcoming unless thoughtful physicians recognize the doubt which shadows the concept of rheumatic fever. The diagnosis of brucellosis is difficult enough when full consideration is given to the possibility.

Summary

A review of the clinical, bacteriologic, immunologic and pathologic findings raises many doubts that "rheumatic fever" is a single disease. At the present time, there is no procedure of any sort that can positively identify rheumatic fever.

Until such time as a diagnostic test for rheumatic fever is available and the problem can be definitely decided, it seems wise to keep an open mind on the question and to investigate thoroughly any reasonable suggestion of a new cause for carditis.

Brucellosis is suggested as a likely cause of chronic valvular heart disease.

REFERENCES

1. Baillou, Guillaume (as translated by Ruhmann, Walter): The earliest book on rheumatism. Brit. J. Rheumat. 2:140, 1940.
2. Haygarth, John: A Clinical History of Diseases. London, Cadell and Davies, 1805.
3. Wells, W. C.: On rheumatism of the heart. Tr. Soc. Improv. Med. & Chir. Knowledge 3:373, 1812. (As reproduced by Willius and Keys: Cardiac Classics. St. Louis, The C. V. Mosby Company, 1941.)
4. Bouillaud, Jean (as translated by Kitchen, James): New Researches on Acute Articular Rheumatism. Philadelphia, Baillière, 1837.
5. Hughes, M. L.: Mediterranean, Malta or Undulant Fever. London and New York, Macmillan and Company, 1897.
6. Jones, T. D.: The diagnosis of rheumatic fever. J.A.M.A. 126:481, 1944.
7. Veale, H.: Report on the cases of fever from Cyprus, Malta and Gibraltar—during the year 1879. Army M. Dept. Report (London) 21:260-276, 1879.
8. Bassett-Smith, P. W.: Some clinical features of Mediterranean fever, with particular reference to cardiac complications. Brit. M. J. 1:313, 1906.
9. Peery, T. M. and Belter, L. F.: Fatal brucellosis: A review of the literature and report of new cases. (To be published.)
10. Peery, T. M. and Evans, J. McC.: Chronic valvular heart disease following nonfatal brucellosis. (To be published.)
11. Amuchastegui, S. R.: Las enfermedades cardiovasculares en el curso de la brucelosis. Rev. Asoc. méd. argent. 62:137, 1948.
12. Hardy, A. V.: Undulant fever: A clinical analysis of 125 cases. J.A.M.A. 92:853, 1929.
13. Huddleson, I. F.: Brucellosis in Man and Animals. New York, Commonwealth Fund, 1939.
14. Spink, W. W.: Clinical aspects of human brucellosis. In: Brucellosis: A Symposium. Washington, D. C., American Association for the Advancement of Science, 1950.
15. Soulèyre, M.: Une forme meningee de la fievre de Malte. Gaz. d. hôp. 83:1655, 1910.
16. Noto, G.: Pachi- e leptomeningite cronica spinale adesiva consecutiva a meningite melitococcica. Riv. di pat. nerv. 40:440, 1932.
17. De Jong, R. N.: Central nervous system involvement in undulant fever. J. Nerv. & Ment. Dis. 83:430, 1936.
18. Lemaire, G., Portier and Bertrand, Ivan: Méningo-encéphalite mélitococcique précoce à évolution rapidement mortelle. Bull. et mém. Soc. med. d. hôp. de Paris 53:712, 1937.
19. Scheidegger, S. and Stern, K.: Encephalitis bei Bangscher Krankheit. Zischr. f. d. ges. Neurol. u. Psychiat. 157:449, 1937.
20. Nichols, Edward: Meningo-encephalitis due to brucellosis. Ann. Int. Med. 35:673, 1951.
21. Harris, H. J.: Brucellosis (Undulant Fever): Clinical and Subclinical. New York, Paul B. Hoeber, 1950, ed. 2.
22. Picard, Joseph: Brucelloses et rhumatismes. Le Concours médical 11:3847, 1951.
23. Simpson, W. M.: Undulant fever (brucelliasis). Ann. Int. Med. 4:238, 1930.
24. Dalrymple-Champneys, Weldon: Undulant fever: A neglected problem. Lancet 1:429-435; 477-485, 1950.
25. Arias, J.: Contribucion al conocimento de la patologia de la brucellosis. An. Fac. med., Lima 34:429, 1951.
26. De Gowin, E. L., Carter, J. R. and Borts, I. H.: A case of infection with Brucella suis, causing endocarditis and nephritis. Am. Heart J. 30:77, 1945.
27. De la Chappelle, C. E.: Vegetative endocarditis due to Brucella melitensis. Am. Heart J. 4:732, 1929.
28. Ross, G.: Brucelosis en la infancia. Rev. chilena de pediat. 22:525, 1951.
29. Levy, D. F. and Singerman, B.: Brucella melitensis bacteremia associated with vegetative endocarditis. Am. Heart J. 15:109, 1938.
30. Beebe, R. T. and Meneely, J. K., Jr.: Brucella melitensis endocarditis. Am. Heart J. 38:788, 1949.
31. Sibel, Nathan and Segal, M. S.: Undulant fever: Two cases simulating subacute bacterial endocarditis and pulmonary tuberculosis. New England J. Med. 212:816, 1935.
32. Harvey, W. A.: Pulmonary brucellosis. Ann. Int. Med. 28:768, 1948.
33. Postelli, T., Altana, G. and Rosa, L.: Un caso di endocardite ulcerosa di natura melitococcica. Cuore e circolaz. 27:117, 1943.
34. Macdonald, R. H.: Acute empyema with Brucella abortus as the primary causative agent. J. Thoracic Surg. 9:92, 1939.
35. Attinger, E.: Febris Undulans Bang unter dem Bilde einer schweren infektiösen Myokarditis. Schweiz. med. Wchnschr. 62:64, 1932.
36. Castaneda, M. R. and Guerrero, Gabriel: Studies on the leukocytic picture in brucellosis. J. Infect. Dis. 78:43, 1946.
37. Waksman, B. H.: The etiology of rheumatic fever; a review of theories and evidence. Medicine 28:143, 1949.
38. Catanzaro, F. J., Stetson, C. A., Morris, A. J., Chamovitz, Robert, Rammelkamp, C. H., Jr., Stolzer, B. L. and Perry, W. D.: The role of the Streptococcus in the pathogenesis of rheumatic fever. Am. J. Med. 17:749, 1954.
39. Paul, J. R. and others: Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects. New York, Metropolitan Life Insurance Company, 1943, ed. 2.
40. Clawson, B. J.: The Aschoff nodule. Arch. Path. 8:664, 1929.
41. Hall, E. M. and Anderson, L. R.: The incidence of rheumatic stigmas in non-rheumatic hearts. Am. J. Path. 18:778, 1942.

Nodular Goiter and Thyroid Cancer

VINCENT M. IOVINE, WILLIAM S. McCUNE, WALTER H. GERWIG AND ALEC HORWITZ*

George Washington University School of Medicine, Washington, D. C.

VINCENT M. IOVINE

WILLIAM S. McCUNE

DURING recent years a number of articles have appeared in the literature dealing with the relationship between nodular goiter and cancer of the thyroid. Among these was a report by Lahey and associates[1] of several cases of thyroid carcinoma which had been preceded by apparently benign adenomas of long standing. These authors indicated that earlier prophylactic removal of these adenomas might have prevented the development of the fatal malignant tumors.

A number of authors have reported the frequency of malignancy in solitary thyroid adenomas and in multinodular goiters. The incidence of malignancy in nodular goiters, as reported in the literature, has varied from 4 per cent found by Brenzier and McKnight[2] to 10.1 per cent reported by Cope et al.[3] More recently, Horn and Dull[4] have indicated an increase in the incidence of malignancy in such lesions treated at the hospital of the University of Pennsylvania from 5.5[5] to 11.4 per cent. The percentage of cancer in nontoxic nodular goiters has uniformly been higher. Although Fisher and Fisher[6] discovered cancer in only 3.7 per cent of such cases, others, notably Crile,[7] reported an incidence of 10.9 per cent and Cole et al.[8,9] as high as 17.1 per cent. Ward[10] found malignancy in only 4 per cent of nodular goiters in women, but in 11 per cent of such goiters in men, a sex distribution similar to that noted by Beahrs, Pemberton and Black.[11,12] Other factors than sex have been suggested as influencing the de-

*Department of Surgery, George Washington University Hospital and School of Medicine, Washington, D. C.

gree of malignancy. Cole, in whose series of 16 cases of carcinoma 70 per cent of the patients died in less than four years, considered the possibility of a geographic variation in invasiveness.

WALTER H. GERWIG

ALEC HORWITZ

Although recently most authors have favored prophylactic removal of all nodular goiters,[13,14] particularly those with solitary nodules, Crile and Dempsey[15] indicated that soft, inconspicuous multiple nodules which do not cause symptoms might be disregarded. Sakal,[16] reviewing the literature, was of the opinion that reports have been of selected cases and that the incidence of malignancy in nontoxic nodular goiters is probably less than 0.2 per cent. He stated further that there is no valid evidence for classifying apparently benign goiters as malignant because they appear to contain single nodules.

In the hope that further clinical investigation may help to resolve these and other questions, we undertook a study to determine the incidence of cancer in persons who were operated on because of the discovery of one or more nodules in the thyroid gland. The cases studied were of 303 patients operated on by us from April 1948 through April 1955. The 303 patients represent a consecutive, unselected group.

We endeavored to determine how and by whom the thyroid nodule was originally discovered. The lesions were of three types in this respect: (1) lesions unknown to the patient which were discovered on a routine examination by a physician; (2) nodules which, either because of symptoms or by accidental discovery, were first noticed by the patient, and (3) lesions in persons who had not had a routine examination or any symptoms, but were told by a neighbor or friend that an enlargement in the neck was noticeable.

We also evaluated the interval from the time of discovery of the nodule to the date of operation. Here, again, the patients studied fall into three categories: (1) those persons who were operated on in less than one month from the time of the original discovery of the nodule; (2) those operated on between one month and one year, and (3) those who waited at least one year or more to have an operation.

Of the 303 patients, 273 or approximately 90 per cent were found to have benign lesions.

TABLE 1

SUMMARY OF FINDINGS IN 303 CASES OF THYROID NODULE

	BENIGN GROUP	MALIGNANT GROUP
Number of cases	273 (89.9%)	30 (10.1%)
Average age of patients	43 years	37 years
Sex distribution:		
Males	15%	13.4%
Females	85%	86.6%
Interval from discovery of lesion to operation:		
One month or less	25%	46.6%
One month to one year	42%	23.3%
One year and over	33%	30.1%
Method of discovery of lesion:		
Routine examination	60%	70%
Noted by patient	30%	26.6%
Other	10%	3.3%

TABLE 2

PATHOLOGIC CLASSIFICATION OF TUMORS

Benign	
Nodular goiter	199
Thyroiditis	22
(Subacute, 3; chronic, 14; Hashimoto's disease, 5)	
Adenomas	37
(Fetal, 20; Hürthle cell, 6; follicular, 11)	
Hyperplastic nodular goiter	10
Cysts	3
Suture granuloma	2
	273
Malignant	
Papillary carcinoma	14
Papillary and follicular carcinoma	7
Follicular carcinoma	6
Follicular and solid carcinoma	1
Hürthle cell carcinoma	1
Nonencapsulated sclerosing carcinoma	1
	30

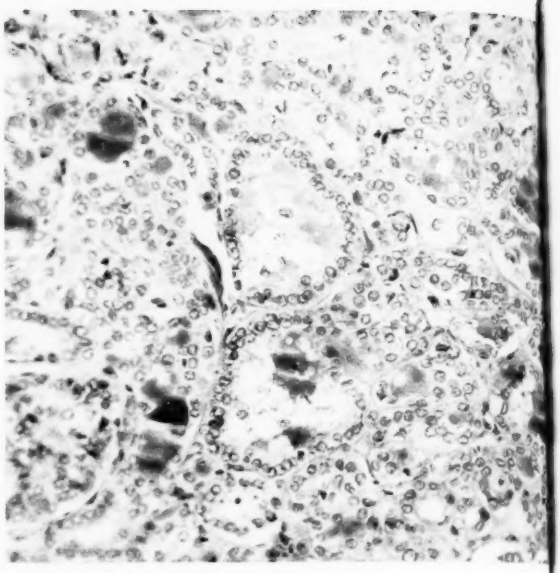


FIGURE 1. Follicular carcinoma of the thyroid.

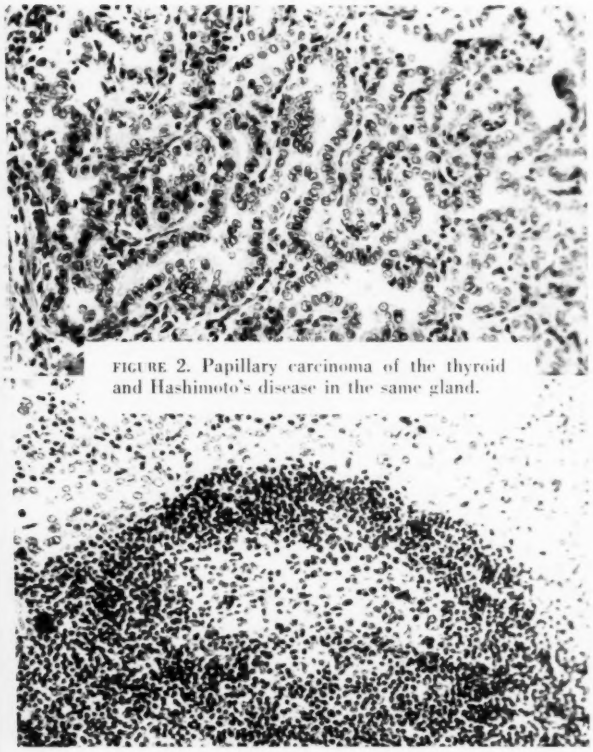


FIGURE 2. Papillary carcinoma of the thyroid and Hashimoto's disease in the same gland.

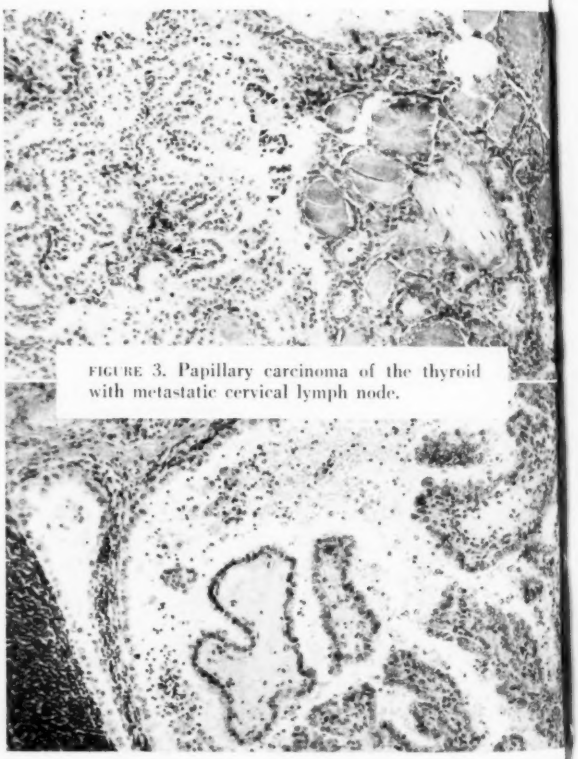


FIGURE 3. Papillary carcinoma of the thyroid with metastatic cervical lymph node.

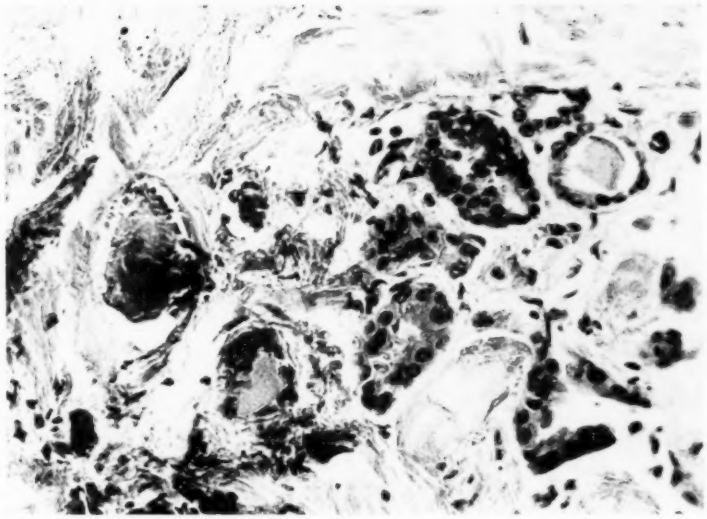


FIGURE 4. Nonencapsulated sclerosing thyroid tumor.

Thirty of the patients had cancer, an incidence of about 10 per cent. The average age of the patients in the benign group was 43 years; that of the group in which cancer was present was 37 years. In both groups, the sex distribution was roughly 85 per cent female and 15 per cent male (table 1).

In both groups, between 60 and 70 per cent of the nodules were first discovered on routine examination by a physician. The remainder were found either by the patient or by a friend. Approximately 65 to 70 per cent of the patients were operated on within one year after discovery of the nodule.

The pathologic classification of the tumors is listed in table 2. Representative types of cancers in the malignant group are illustrated in figures 1 to 4.

The importance of routine examinations is borne out by the fact that nearly 70 per cent of these lesions were discovered in this manner. We believe that a 10 per cent incidence of malignancy in thyroid nodules, more than two-thirds of which were discovered by physicians, emphasizes the importance of routine examination. Moreover, in our opinion, this high incidence of malignancy emphasizes the urgency for surgical investigation of all thyroid nodules. Since less than one-third of our patients came to operation within one month after discovery of the nodule, the need for earlier surgery is evident.

REFERENCES

1. Lahey, F. H., Hare, H. F. and Warren, S.: Carcinoma of the thyroid. Ann. Surg. 112:977-1005, 1940.
2. Brenzier, A. G. and McKnight, R. B.: True adenomas of the thyroid gland and their relation to cancer. Tr. Am. A. Study Goiter, 1940, p. 176.
3. Cope, O., Brown, D., Hamlin, E. and Hopkink, J.: What thyroid nodules are to be feared? J. Clin. Endocrinol. & Metab. 9:1012, 1949.
4. Horn, R. C., Jr. and Dull, J. A.: Carcinoma of the thyroid, a reevaluation. Ann. Surg. 139:35, 1954.
5. Horn, R. C., Jr., Welty, R. F., Brochs, F. P., Rhoads, J. and Pendergrass, E. P.: Carcinoma of the thyroid. Ann. Surg. 126:140-168, 1947.
6. Fisher, E. R. and Fisher, B.: Nodular goiter and carcinoma of the thyroid. Am. J. Surg. 82:202, 1951.
7. Crile, George, Jr.: Papillary carcinoma of the thyroid and lateral cervical region. Surg., Gynec. & Obst. 85:757-766, 1947.
8. Cole, W. H., Majarkis, J. D. and Slaughter, D. P.: Carcinoma in nodular goiter. J. Clin. Endocrinol. & Metab. 9:1007, 1949.
9. Cole, W. H., Slaughter, D. P. and Rossiter, L. J.: Potential dangers of nontoxic nodular goiter. J.A.M.A. 127:883-888, 1945.
10. Ward, R.: Symposium on surgical lesions of the thyroid; malignant goiter. Surgery 16:783-803, 1944.
11. Pemberton, J. de J. and Black, B. M.: Cancer of the Thyroid. New York, American Cancer Society, 1954.
12. Beahrs, O. H., Pemberton, J. de J. and Black, B. M.: Nodular goiter and malignant lesions of the thyroid gland. J. Clin. Endocrinol. 11:1157, 1951.
13. Eckert, C. and Byars, L. T.: The surgery of papillary carcinoma of the thyroid gland. Ann. Surg. 136:83, 1952.
14. Hinton, J. W. and Lord, J. W.: Is surgery indicated in all cases of nodular goiter, toxic and nontoxic? J.A.M.A. 129:605-605 (October 27) 1945.
15. Crile, George, Jr. and Dempsey, W. S.: Indications for removal of nontoxic, nodular goiter. J.A.M.A. 139:1247, 1949.
16. Sakal, J.: Incidence of malignancy in toxic and nontoxic nodular goiter. J.A.M.A. 154:1321-1325, 1954.

Physiologic Basis for Rational Therapy in Chronic Pulmonary Emphysema

JAMES J. FEFFER AND JAMES P. MANN*

George Washington University School of Medicine, Washington, D. C.

OBSTRUCTIVE pulmonary emphysema, a chronic, disabling and relentlessly progressing disease, is being recognized today with increasing frequency. A better understanding of the pathophysiology of this condition has opened the way to a logical therapeutic approach and to a favorable alteration in the clinical manifestations and functional abnormalities. There is abundant evidence that a considerable portion of the disability in emphysema results from disturbed pulmonary physiology and not from organic changes.[1]

On the basis of a series of 100 consecutive cases seen in private practice, we shall attempt to demonstrate the clinical reversibility of chronic pulmonary emphysema. These 100 patients were followed for from two months to nine years with an average follow-up of 17 months. There were 69 males and 31 females.

Eighty per cent of the male patients and 60 per cent of the female patients presented clinical, radiographic and functional evidence of advanced emphysema. The fact that emphysema may exist long before typical x-ray changes occur was borne out by findings in 26 per cent of this group. Thirteen per cent demonstrated a typical asthmatic picture with acute episodes of dyspnea and wheezing. However, in 77 per cent the history was that of chronic bronchitis—continuous cough, wheezing and insidiously progressing dyspnea. In only four of the patients was there exclusively seasonal aggravation of symptoms.

JAMES J. FEFFER

JAMES P. MANN

Ten patients had so-called primary emphysema, which we feel is an entity distinct from emphysema secondary to bronchospastic disease. In primary emphysema the initial pre-

*Department of Medicine, George Washington University School of Medicine, Washington, D. C.

TABLE 1

AGE DISTRIBUTION AT ONSET OF SYMPTOMS AND WHEN FIRST STARTED ON INTENSIVE THERAPY

	DECADE							TOTAL
	First	*Second*	*Third*	*Fourth*	*Fifth*	*Sixth*	*Seventh*	
Onset of symptoms	34	9	14	17	13	10	3	100
Intensive therapy	13	6	3	16	24	20	18	100

senting complaint is dyspnea unassociated with significant amounts of wheezing.

With few exceptions, all the patients previously had been exposed to many therapeutic programs including desensitization therapy. The onset of symptoms (table 1) occurred during the first four decades of life in 74 per cent of the patients, whereas intensive therapy was started prior to age 40 in only 38 per cent.

Pathophysiology

The basic abnormality appears to be obstruction to expiratory air flow in an individual with a hereditarily irritable bronchial tree. The obstruction is due to three factors in combination. The first is a spasm of the walls of the smaller bronchi and bronchioles, evidence for which comes entirely from physiologic and clinical observations. From a practical standpoint, however, this evidence is sufficiently conclusive to serve as a basis for treatment.[2] The second factor is an edema of the respiratory mucosa, which has been clearly demonstrated pathologically, and the third is the presence of increased secretions, produced by the mucous and goblet cells and ultimately presenting itself as sputum. Each of these components tends to reduce the size of the bronchial lumina (figure 1).

Physiologically, the bronchi dilate during inspiration, whereas during expiration they contract. Thus any obstruction would be exaggerated during exhalation and would make it more difficult to expel air from the lungs than to take it in. The obstruction is elicited clinically by listening for predominantly expiratory wheezing, which may be demonstrable only during rapid expiration or on repeated auscultation. Ninety-seven per cent of the patients in this series demonstrated sibilant rales on auscultation.

These four factors (bronchial spasm, mucosal edema, increased secretions and physiologic expiratory narrowing) make it impossible to expel all the inspired air from the lungs and consequently result in "trapping," which can be demonstrated conclusively by spirographic tracings. Significant incomplete or delayed emptying was demonstrated in these patients by timed vitalometer studies (table 2) and by chest x-rays taken in full inspiration and expiration.

Nebulization Therapy

Nebulization therapy, when used correctly, relieves bronchial obstruction effectively. The selection of an aerosol with optimal particle size for therapeutic administration depends

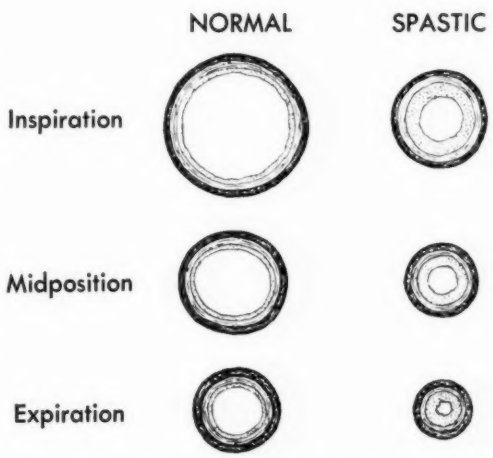


FIGURE 1. Cross-sectional views of smaller bronchi and bronchioles (semidiagrammatic).

TABLE 2

PRETREATMENT TIMED VITALOMETER STUDIES
(Average of 28 Cases)

One second vital capacity (normal over 83 per cent) *	57 per cent of total vital capacity
Two second vital capacity (normal over 94 per cent) *	67 per cent of total vital capacity
Total vital capacity	62 per cent of predicted vital capacity†

*Gaensler, E. A.: Analysis and critique of pulmonary function studies. Bull. New England M. Center 13:49-61, 1951.

†Based on height and weight according to DuBois' body surface formula and West's normals of 2.5 liters per square meter for men and 1.9 liters per square meter for women.

on the location where deposition is desired. In the treatment of bronchospasm it is necessary to use an aerosol of relatively small particle size in order to obtain local application to the smaller bronchi. Furthermore, irritating deposition of drugs on the pharynx, larynx and trachea occurs when large particle sizes are inhaled.[3] The nebulizer should produce an average particle size of 1 to 3 microns.

The breathing pattern of the subject also affects distribution. Inhalation through the mouth alone results in better distribution in the lungs than inhalation through the nose.[4] Areas of turbulence in the nasal passages cause deposition and loss of the drug in substantial amounts in the nose, sinuses and nasopharynx. The expiratory-inspiratory pause method of inhalation should result in greater subjective and objective improvement.[5]

The nebulizer should be equipped with a face mask and rebreathing bag (figure 2) and it must be energized by gas under pressure. Hand-operated devices are unsatisfactory because of the relatively large volume of solutions required to bathe the bronchial mucosa. Compressed oxygen or an electric air compressor with flows of approximately 4 liters per minute provides uniform particle size.

The most effective method of nebulization therapy currently available utilizes intermittent positive pressure equipment. It is, however, an expensive operation and its additional benefits appear primarily in patients with severe, advanced ventilatory insufficiency. In these situations the patient's poor ventilatory exchange does not permit an adequate bathing of the bronchial mucosa with simple nebulization equipment, and positive pressure therapy should be used for best results.

The Bennett and the Emerson pressure therapy units have been used with equal success. These units simultaneously administer a gas and any desired aerosol. Their pressure characteristics are such that they provide a slowly rising inspiratory pressure and a rapidly falling expiratory pressure which promote the movement of sputum from the smaller to the larger bronchi. The instantaneous flow rate is adequately high for all dyspneic patients. The "flow-sensitive" and "pressure-sensitive" valves make it possible for the patient to exhale to the limit of his ability before a new inspiratory cycle is begun. Nonpressurized therapy with a Pen-i-sol nebulizer (figure 2) was used in 64 patients, IPPB therapy was employed in 20 patients, and 16 patients did not receive inhalation therapy.

Continuous nebulization therapy occasionally is indicated in a case of an emphysema-

FIGURE 2. No. 200 Universal Pen-i-sol unit (Hudson Oxygen Therapy Sales Company, Los Angeles 27, California).

tous patient with acute suppurative bronchitis or pneumonitis. It can be adequately provided by a Mist-O-Gen*-like generator. The addition of glycerin (2.5 per cent) alters the vapor pressure of water solutions, thereby prolonging the survival of the individual droplets. Propylene glycol produces a more stable and longer lasting aerosol.

Antibiotics increase the danger of sensitization and there is no convincing evidence that inhalation is better than oral or parenteral administration. Nebulization of antimicrobial agents is certainly to be avoided in patients with a hypersensitivity background and it is only rarely indicated in patients with chronic obstructive emphysema.

Sympathomimetic drugs—Those which are most effective in interrupting bronchial spasm and mucosal edema are derivatives of phenylethylamine (table 3). Many are commonly used by nebulization but all are similar in action to one of the following:

1. Epinephrine, the prototype sympathomimetic agent (commonly used as the levorotatory isomer) causes both contraction of bronchial mucosal blood vessels and relaxation of bronchial smooth muscle. However, because of its central nervous system and cardiovascular toxic effects, it is not the most satisfactory drug. Racemic epinephrine (VAPONEFRIN® 2.5 per cent) produces a greater immediate and a more prolonged effect than epinephrine. (The dextrorotatory isomer is less active pharmacologically.)

2. Isopropylarterenol (ALUDRINE®, ISUPREL®, NORISODRINE®) is more potent than epinephrine as a bronchial relaxant and myocardial stimulant. It occasionally produces symptomatic and electrocardiographic evidence of coronary insufficiency, and caution is warranted in its use for patients with myocardial disease. It lacks the decongestive action of epinephrine and should be used only in conjunction with a substance such as phenylephrine. Clinically, a patient may respond better to one of these three (levorotatory epinephrine, racemic epinephrine or isopropylarterenol) than the other. Refractoriness is not transferable and alternation may be helpful.

3. Phenylephrine (NEO-SYNEPHRINE®, levorotatory) produces vasoconstriction without cardiac or central nervous system stimulation. "Fastness," as with epinephrine or Isuprel, and significant rebound congestion, as with PRIVINE®, do not occur.

TABLE 3

Sympathomimetic drugs

1. Epinephrine, 1 per cent, used as levorotatory isomer (Vaponefrin [racemic epinephrine] 2.5 per cent)
2. Isopropylarterenol (Isuprel, Aludrine, Norisodrine), 0.5 to 1 per cent
3. Phenylephrine (Neo-synephrine, levorotatory), 1 per cent

Parasympathomimetic drugs

1. Antrenyl (diethyl methylammonium bromide), 0.5 mg. per cubic centimeter
2. Pamine (methscopolamine bromide)
3. Dylephrin (racemic epinephrine 2.5 per cent, atropine 0.5 per cent)

Parasympathomimetic drugs—Although adrenergic stimulation is effective, it might be inferred that this approach directed toward overcoming a continuing bronchoconstrictor stimulus is less physiologic than one directed toward the actual blocking of the stimulus. It would therefore appear advantageous to attempt to neutralize a cholinergic phenomenon, namely, bronchospasm, mediated by cholinergic influences, by cholinergic blockade. In our experience the available parasympathomimetic drugs—ANTRENYL® (diethyl methylammonium bromide) 0.5 mg. per cubic centimeter, PAMINE® (methscopolamine bromide) and DYLEPHRIN® (racemic epinephrine 2.5 per cent, atropine 0.5 per cent)—have not been as useful as the sympathomimetic drugs, but occasionally they are helpful.

Evacuation of Bronchial Secretions

Liquefaction of retained secretions is necessary for their evacuation. Among the expectorants, potassium or sodium iodide salt (0.6 gm. t.i.d.) is probably the most effective

*Mist-O-Gen Equipment Division, Production Foundry Company, Oakland 7, California.

liquefying agent. Hydriodic acid is used principally in pediatric practice. Glycerol guaiacolate (0.1 to 0.2 gm. t.i.d.) is also a very satisfactory expectorant.

Detergents or wetting agents decrease viscosity of secretions which interfere with the normal mechanism of bronchial cleansing. These agents reduce surface tension, have a mild bacteriostatic effect, and promote the loosening of sputum. They are best used by continuous nebulization and they may be combined with bronchodilators. The most satisfactory agents are: triton WR-1339 (ALEVAIRE®), cetyl pyridinium (CEEPRYN®) (1:1000), ZEPHIRAN® aqueous (1:1000), 0.1 per cent, and THRONZONIUM® bromide (1:500), 0.2 per cent.

Enzymes have also been used within the tracheobronchial tree for the lysis of tenacious sputum. Crystalline trypsin (TRYPTAR®) is dissolved in Sorensen's phosphate buffer solution with a pH of 7.1 (100,000 units per cubic centimeter); 50,000 units are used the first day, 100,000 units the second day, and 200,000 units per day thereafter. BENADRYL®, 50 mg., given before the treatment will eliminate most reactions—dyspnea, chills and fever. Tolerance is acquired and reactions are rare after the third or fourth day of treatment. Its mucolytic action has been demonstrated in vitro and in vivo. An enzymatic débridement of the entire respiratory system is claimed by some investigators,[6] but our results have been disappointing. Pancreatic DORNASE® (100,000 units per 2 cc. Sorensen's phosphate buffer solution) has a similar effect.

Postural drainage remains a most important method of evacuating secretions, as do effective coughing and tracheal aspiration. Dehydration increases the viscosity of bronchial secretions and interferes with drainage. Local hydration actually can be accomplished by appropriate continuous nebulization.

Infection

Patients with emphysema are unusually susceptible to recurrent bouts of acute bronchitis and bronchopneumonia, as well as to low grade chronic bronchial suppuration. Bronchial obstruction is thereby increased and alveolar ventilation is further diminished, leading at times to acute anoxia and carbon dioxide retention.[7]

It is vital that daily observations of sputum color be made by the patient. Any change from egg white to creamy, yellow, gray or green is an indication for antimicrobial therapy. When originally seen, 33 per cent of this group of patients presented a history of predominantly purulent sputum, 42 per cent a history of predominantly nonpurulent sputum, and 25 per cent a history of nonproductive cough.

The choice of the antimicrobial agent ideally should depend on the predominating organisms, their sensitivities and the patient's

TABLE 4

STEROID THERAPY CASES (79) *

		EOSINOPHILIA†	NO EOSINOPHILIA
Definite improvement	55 (70%)	46 (84%)	9 (16%)‡
Nonspecific improvement	8 (10%)	3 (37%)	5 (63%)
No improvement	16 (20%)	1 (6%)	15 (94%)
TOTAL	79	50	29

*Five additional patients on whom an eosinophil count was not made received steroids. Four of these demonstrated definite improvement and one, no improvement.

†Total eosinophil count of more than 350 per cubic millimeter (89 per cent over 500, 78 per cent over 700, 13 per cent over 1000).

‡Two patients had personal histories of nasal polyps, seasonal rhinitis, hay fever and/or hives. Two patients had family histories of asthma, wheezing, bronchitis and/or hay fever.

tolerance to the drug. From a practical standpoint, the broad-spectrum antibiotics can be used with success in most cases without sensitivity studies. If a completely satisfactory response (i.e., reduction of sputum to a small amount of mucoid material) is not obtained, sensitivity studies are indicated. In this group of patients resistance has been demonstrated occasionally to all drugs except CHLOROMYCETIN® and erythromycin. In these situations one should not hesitate to use Chloromycetin, accepting the small calculated risk of aplastic anemia. GANTRISIN®, which is considerably cheaper than the broad-spectrum drugs, has proved effective in many cases. In resistant *Aerobacter aerogenes*, *Pseudomonas aeruginosa* and *Proteus vulgaris* infections, polymyxin B (250,000 units, 25 mg. q.i.d.) by nebulization is at times effective without exposing the patient to the nephrotoxic effects of parenteral administration.

Hormone Therapy

Corticotropin, cortisone and hydrocortisone do not alter the basic disease. However, they can be very helpful in interrupting bronchial spasm and mucosal edema. It is obvious (table 4) that a dramatic response to these agents can be anticipated when peripheral eosinophilia is present, and the more severe the eosinophilia, the more dramatic the response. To the contrary, a normal peripheral eosinophil count strongly suggests that no response to these hormones will occur. However, even in the absence of eosinophilia, a patient with a history of nasal polyps or hay fever, or with a strong family history of hypersensitivity phenomena, will sometimes have a good response. The precise mechanism involved is not known. The effect apparently depends on a nonspecific factor of unknown character. Fifty per cent of the patients had eosinophilia and all of these were given steroids. Twenty-nine patients without eosinophilia were tried on steroids either because of a hypersensitivity background or empirically because other therapeutic measures were not entirely successful. Steroids were not given to 16 of the patients who did not have eosinophilia.

Those patients who respond favorably are continued on a maintenance dose (average, 20 to 40 mg. HYDROCORTONE® daily). This dose is regulated by the level at which eosinophilia recurs, as well as by the level at which signs and symptoms of bronchial obstruction return. Recently, oral Hydrocortone and METICORTEN® have been used almost exclusively. Hydrocortone produces a more dramatic eosinopenia than cortisone, and from preliminary observations Hydrocortone seems to produce a better clinical response than Meticorten.

Polycythemia

The hematologic adaptation to anoxia which occurs at high altitude is a less constant feature in emphysema. Furthermore, in emphysema the degree of adaptation does not parallel the degree of anoxia. Wilson et al.[8] have demonstrated that the only constant change in emphysema is an increase in red blood cell size. The bone marrow is normal and the peripheral reticulocyte count is not significantly increased. There is an increase in mean corpuscular volume and a decrease in mean corpuscular hemoglobin. They demonstrated a high inverse correlation between arterial oxygen and mean corpuscular volume, and concluded that the increased cell size appears to be related to anoxia. Isolated patients with emphysema do have a marked increase in hemoglobin and in numbers of red blood cells. However, if one is to accept the results of the aforementioned investigation, elevated hematocrits in emphysema are the result of increased red cell mass rather than increased red cell number.

It is widely accepted that "polycythemia" is a rare finding in emphysema. However, hematocrit determinations in this series revealed that 34 per cent of the patients had a cell pack of 50 per cent or more and 21 per cent had a cell pack of 52 per cent or more. There was no correlation between the degree of functional and anatomic change and the degree of increase in packed cell volume. Perhaps it would be better to refer to this increased hematocrit as increased "red cell mass" rather than as polycythemia.

Phlebotomy was done routinely when the hematocrit was over 50 per cent, and, in fact,

TABLE 5

RESULTS OF VENTILATORY STUDIES (IN LITERS)
(28 Consecutive Patients)

CASE	PREDICTED TOTAL VITAL CAPACITY	PRETREATMENT TOTAL VITAL CAPACITY	POST-TREATMENT TOTAL VITAL CAPACITY	PRETREATMENT ONE SECOND VITAL CAPACITY	POST-TREATMENT ONE SECOND VITAL CAPACITY
1	5.1	4.1	4.3	2.9	3.1
2	4.1	1.4	2.5	0.7	1.7
3	4.5	3.8	3.3	2.2	1.5
4	3.0	1.8	3.0	1.0	2.0
5	4.3	1.4	1.4	0.4	0.5
6	2.6	2.2	2.3	1.4	1.7
7	3.6	1.3	1.6	0.9	1.1
8	3.4	2.7	2.8	2.1	2.4
9	4.3	1.5	2.5	0.8	0.9
10	3.0	2.4	2.8	1.0	1.1
11	4.0	1.6	2.5	1.3	2.1
12	4.9	3.9	3.8	1.4	2.0
13	5.0	3.3	3.7	1.9	2.3
14	4.9	1.9	2.7	0.9	1.4
15	4.2	2.5	2.9	1.0	1.7
16	2.9	1.6	1.9	0.7	1.4
17	5.3	2.3	3.5	1.0	1.6
18	2.9	2.0	2.0	0.9	1.4
19	5.0	4.1	4.4	3.2	3.0
20	3.1	2.2	2.8	1.4	1.6
21	3.2	2.7	2.9	2.0	2.0
22	4.6	2.6	3.7	0.6	1.5
23	5.0	3.6	3.7	2.4	2.9
24	3.2	2.8	2.9	2.3	2.4
25	3.0	2.1	2.1	0.9	1.7
26	3.1	2.3	2.5	2.0	1.9
27	3.2	1.4	2.1	0.8	1.5
28	4.7	2.2	3.1	0.9	1.3

when the hematocrit was over 45 per cent in patients who were not adequately responding to therapy. An attempt was made to maintain a packed cell volume of 45 per cent or slightly lower.

Anoxia in patients with emphysema is always associated with hypervolemia. Reducing blood volume in patients will provide additional benefit largely through reducing pulmonary artery pressure and blood volume.[9]

Cor Pulmonale

The physiologic abnormalities in cor pulmonale are well known. Twenty-three per cent of this group of patients had cor pulmonale with congestive failure as demonstrated by peripheral edema, enlarged liver, elevated venous pressure, and response to cardiac therapy. In no instance was there evidence for other causes of congestive failure. Nineteen patients were digitalized and 13 (68 per cent) were definitely improved as a specific result of digitalization and administration of diuretics, sodium restriction and phlebotomy.

Respiratory Acidosis

In emphysema the hypoxic stimulus is largely responsible for maintaining the rate of respiration and tidal exchange. This stimulus is removed if oxygen or sedation is administered. The principal cause of acidosis is ineffective alveolar ventilation produced by heavy sedation, abrupt correction of chronic hypoxia or acute respiratory infection. Treatment includes prevention as well as active management of existing acidosis. The goal is to restore good alveolar ventilation. It is to be emphasized, however, that respiratory acidosis will occur only rarely if proper consideration is given to the existing physiologic ab-

normalities. In this group of 100 patients acidosis of clinical significance developed in only two patients, one because he was inadvertently placed in an oxygen tent by a house physician and the other because of a severe, resistant pulmonary infection.

Oxygen should be administered only by nasal catheter, starting with a flow rate of no more than 1 liter per minute and increasing no more rapidly than 1 liter per day. For established respiratory acidosis, artificial respiration should be induced mechanically with a chamber respirator. Opiates are contraindicated, and DEMEROL® or other sedatives should be used judiciously. Antimicrobial agents should be prescribed routinely for infection. DIAMOX® may be helpful by reducing arterial carbon dioxide tension.[10]

Diaphragmatic Function

Breathing exercises will improve ventilatory efficiency. Increased diaphragmatic excursion can be developed by special training and daily practice. Careful attention was given to all patients requiring such training. Emphysema belts which cause diaphragm elevation through abdominal compression were found to be helpful only in "potbellied" individuals. The use of pneumoperitoneum has been almost completely abandoned because the associated discomfort outweighed its questionable benefits.

Results

In the 28 cases in which the patients were subjected to ventilatory studies the average increase in the amount of air that could be exhaled in one second was 400 cc. (table 5). In 13 (46 per cent) the increase was over 500 cc., and in eight (30 per cent), over 700 cc. Because of the concomitant improvement in total vital capacity (average 400 cc.) the one second-timed vital capacity percentage does not reflect the true benefits derived from therapy. The significant factor in obstructive emphysema, however, is the amount of air that can be exhaled in a limited time rather than the relationship between this factor and the total vital capacity.

In an attempt to grade the pretreatment disability and response to therapy, the following classification was arbitrarily established:

Group I—No symptoms or physical limitation (applies only to post-treatment status).

Group II—Dyspnea with respiratory infections only—no symptoms or physical limitation at other times.

Group III—Mild constant exertional dyspnea requiring some restriction in physical activity.

Group IV—Severe exertional dyspnea—sedentary work only.

Group V—Dyspnea at rest—total physical disability.

It will be noted (table 6) that 61 per cent of the male patients and 27 per cent of the female patients fell into groups IV and V before treatment. It will also be seen that a good response (advanced two or more grades) to intensive therapy occurred in 51 per cent of the patients, a moderate response (advanced one grade) in 21 per cent, a slight response (symptomatic improvement in grade) in 16 per cent, and no improvement or regression in 12 per cent.

Discussion

It is important to realize that there is no single therapeutic agent available which will produce satisfactory results in the manage-

TABLE 6

CHANGE IN DEGREE OF DISABILITY AND RESPONSE TO INTENSIVE THERAPY (100 Patients)

GRADE*	PRETREATMENT STATUS			POST-TREATMENT STATUS
	Male	*Female*	*Total*	*Total*
V	13	1	14	9
IV	30	7	37	12
III	12	14	26	10
II	14	9	23	39
I	0	0	0	30

RESPONSE	CASES
Good (advanced two or more grades)	51
Moderate (advanced one grade)	21
Slight (symptomatic improvement in grade)	16
None (stable or regressed)	12
TOTAL	100

*See text.

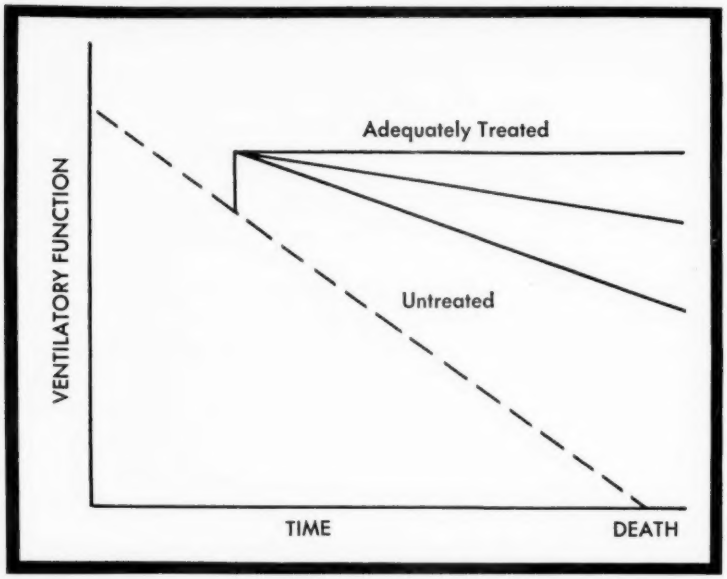


FIGURE 3. Course of adequately treated and untreated obstructive pulmonary emphysema.

ment of chronic pulmonary emphysema. An adequate therapeutic program must utilize a combination of methods selected to fit the needs of the individual patient. Careful evaluation of the history, physical findings and results of simple laboratory procedures (hematocrit, total eosinophil count, etc.) will provide the information necessary for initiating an intensive, continuous program of therapy. Failure to prevent the progressive dissipation of pulmonary function characteristic of untreated or poorly treated emphysema is most often due to one or more of the following factors: (1) failure to recognize low grade, chronic bronchial infection; (2) failure to recognize the need for daily inhalation therapy; (3) failure to recognize that even in the absence of symptoms, low grade expiratory bronchial obstruction will result in progressive loss of ventilatory function.

Conclusions

Physiologically directed therapy involves the use of procedures which restore or maintain the function of the respiratory system. In obstructive emphysema, favorable alterations in the pathophysiologic abnormalities may lead to marked improvement in respiratory function. Life expectancy will be increased (figure 3) in practically all of the adequately treated patients and the majority will experience significant improvement in exercise tolerance.

REFERENCES

1. DONALD, K. W.: The definition and assessment of respiratory function; part I. Brit. M. J. 1:415, 1953.
2. HERSCHFUS, J. A., BRESNICK, E. and SEGAL, M. S.: Pulmonary function studies in bronchial asthma. II. After treatment. Am. J. Med. 14:34, 1953.
3. BARACH, A. L., BICKERMAN, H. A. and BECK, G. J.: Antibiotic therapy in infections of the respiratory tract. Arch. Int. Med. 90:808, 1952.
4. BARACH, A. L., GARTHWAITE, B. and BICKERMAN, H. A.: Studies on aerosol deposition. Postgrad. Med. 5:341, 1948.
5. MILLER, W. F.: A consideration of improved methods of nebulization therapy. New England J. Med. 251:589, 1954.
6. LIMBER, C. R., REISER, H. G., ROETTIG, C. L. and CURTIS, G. M.: Enzymatic lysis of respiratory secretions by aerosol trypsin. J.A.M.A. 149:816, 1952.
7. BEALE, H. D., SCHILLER, I. W., HALPERIN, M. H., FRANKLIN, W. and LOWELL, F. C.: Delirium and coma precipitated by oxygen in bronchial asthma complicated by respiratory acidosis. New England J. Med. 244:710, 1951.
8. WILSON, R. H., BORDEN, C. W. and EBERT, R. V.: Adaptation to anoxia in chronic pulmonary emphysema. Arch. Int. Med. 87:581, 1951.
9. GLASER, E. M. and MCMICHAEL, J.: The effect of venesection on capacity of the lungs. Lancet 2:230, 1940.
10. HEISKELL, C. L., JR., BELSKY, J. B. and KLAUMANN, B. F.: Treatment of chronic emphysema of lungs with Diamox. J.A.M.A. 156:1059, 1954.

Side Effects of Antibiotic Therapy

JOHN P. NASOU* AND MONROE J. ROMANSKY**

George Washington University School of Medicine, Washington, D. C.

ALTHOUGH complications in the course of antibiotic therapy are relatively infrequent when compared with the widespread use of these agents and the benefit derived, nevertheless such comparative statistics find little application in the treatment of any one patient. Emphasis, therefore, must be placed on these reactions and their severity as they do occur. This is not meant to disparage or discourage the proper use of the antibiotics, but to bring attention to the need for preventing such complications and the necessity for the ever-discriminating use of these potent agents.

The complications of antibiotic therapy may be classified as follows: (1) toxicities innate to the antibiotics, (2) complications incident to the host's response to antibiotic therapy and (3) host complications incident to the responses of microorganisms during antibiotic therapy.

1. Innate Toxicities

At present, 14 antibiotics are in commercial production. These can be divided roughly into two groups, those in common use and those whose use is restricted because of one or more undesirable properties (table 1).

JOHN P. NASOU

MONROE J. ROMANSKY

For the sake of convenience, the innate toxicities of these antibiotics are presented in table form (table 2). "Drug fever" may occur with any of these agents. Those antibiotics marked with an asterisk in table 2 are good for use in local preparations, because of their low sensitizing potential and the fact that they are only occasionally used parenterally.

2. Complications Incident to Host's Response

The sensitivity reactions to antibiotics have attracted the greatest attention of all, probably because they are the least predictable and

*Lieutenant (SG), M.C., U. S. Navy Reserve.

**Department of Medicine, George Washington University School of Medicine; George Washington University Medical Division, District of Columbia General Hospital, Washington, D. C.

TABLE 1

ANTIBIOTICS IN COMMERCIAL PRODUCTION

Common use	*Restricted use*
Penicillin	Bacitracin
Streptomycin	Chloramphenicol
Dihydrostreptomycin	Neomycin
Oxytetracycline	Polymyxin
Chlortetracycline	Viomycin
Tetracycline	Tyrothricin
Erythromycin	
Carbomycin	

commonest of the antibiotic complications. Kern[1] presented the following factors as operating in the production of antibiotic sensitivity.

First, and probably most important, is a sensitizing exposure. The history in most cases of allergic reactions confirms that there is usually previous contact with the antibiotic.

Second in importance is an allergic constitution. Allergists estimate that 15 per cent of the population have a predisposition to allergy; therefore, one out of every seven patients is a potential candidate for such sensitization. Reports as to whether antibiotic sensitization is more common in patients with other allergies are conflicting.

The third factor is the antibiotic preparation and route of administration. Generally, local application, including troches and lozenges, is most likely to produce sensitization. Parenteral administration is the next most frequent cause. The oral route is least likely to favor the production of sensitivity. Certain preparations also are more allergenic than others. The iodide derivative of penicillin, marketed as NEO-PENIL®, has been especially responsible for a great many severe reactions.

Fourth are cross-reactions with the products of other fungi. There are many cases of penicillin sensitivity in which there is no history of previous contact with the drug. It has been proposed that these patients are reacting to the allergy produced by previous fungous infections, such as epidermophytosis. This concept has been strengthened by recurrence of "id" eruptions in some patients who are receiving antibiotics.

Skin manifestations—The true incidence of cutaneous allergic phenomena due to penicillin is difficult to ascertain. The incidence reported in various series ranged from 2 to 10 per cent, the majority tending toward the lower figure. Many patients probably have skin reactions of a minor character, do not associate them with the antibiotic, and do not report them to their physician.

The three main types of skin reactions due to penicillin are urticaria, vesicular reactions and exfoliative dermatitis, in order of their frequency. Other reactions occurring less frequently include erythema, maculopapular rashes and erythema nodosum or multiforme. Exfoliative dermatitis may be so severe as to cause death.

Streptomycin is second only to penicillin in causing skin reactions. These are frequently mild maculopapular reactions which may escape detection, but any of the skin reactions mentioned under penicillin may occur. Streptomycin allergies cross-react with dihydrostreptomycin.

Skin reactions of an allergic character are rare with the so-called broad-spectrum antibiotics. The few that have been reported occur as fixed eruptions or urticaria, are mild, and promptly subside on cessation of therapy.

This type of sensitization has also been felt by the medical and nursing personnel of hospitals and by individuals engaged in the manufacture of antibiotics. Care should be taken in mixing and administering antibiotics to avoid contact with the skin.

Anaphylaxis—Anaphylaxis is perhaps the most alarming complication of antibiotic therapy. This is usually an immediate reaction (a few seconds to a few hours after administration), characterized by any or all of the following: urticaria, angioneurotic edema, asthma, labored breathing, shock, cyanosis and unconsciousness. Death may occur from two minutes to several hours after onset.

In the first nine years that penicillin had been in use, only two fatalities were noted. In the next one and a half years, 15 additional anaphylactic fatalities were reported. More

TABLE 2

INNATE TOXICITIES OF THE ANTIBIOTICS

ANTIBIOTIC	TOXICITY	OTHER FACTORS
Penicillin	5000 to 10,000 units per milliliter applied to brain tissue may produce focal or generalized convulsions	Massive intravenous doses may produce concentrations in the blood of 5000 units per milliliter
Streptomycin Dihydrostreptomycin	Ototoxic: auditory and vestibular nerve damage	(1) Diminished by the use of mixture of the two forms. (2) High blood concentrations obtained in presence of kidney damage; use with care
Chloramphenicol	Rarely may produce agranulocytosis, aplastic anemia. (Others as under tetracycline series, with lesser frequency)	Particularly effective with erythromycin in staphylococcal infections
Tetracycline series Oxytetracycline Chlortetracycline Tetracycline	Nausea and vomiting. Anorectal effects —pruritis ani, fissures, proctitis, ulcerative colitis	Do not use antacids of aluminum hydroxide type to counteract; they impair absorption of antibiotic. Coadministration of milk, buttermilk, yogurt, B complex of questionable value
	Hepatoxicity or renal toxicity	Occasionally and only with high doses
Erythromycin	Occasional abdominal cramping	Relieved by belladonnalike drugs
Carbomycin	Inadequate use to evaluate—rare to present	
Viomycin	Nephrotoxic, ototoxic	Substitute antituberculous agent—1 to 2 gm. twice a week. Minimal toxicity with this dose
Bacitracin*	Nephrotoxic	Contraindication if any kidney damage is present
Neomycin*	Nephrotoxic, ototoxic	May be used when sensitivity tests show it to be the only effective antibiotic
Polymyxin*	Nephrotoxic, paresthesias	Parenterally 2.5 mg. per kilogram primarily for *Pseudomonas* infections which are resistant
Tyrothricin*	Hemolytic	Never parenterally

*Good for use in local preparations because of low sensitizing potential and the fact that they are only occasionally used parenterally.

fatalities probably have occurred but have not been reported in the literature. Anaphylaxis has been reported as a result of practically all forms of penicillin and by every route. The iodide salt of penicillin, penethamate hydriodide or Neo-Penil, is especially dangerous. In the six months after its introduction and while not as yet in widespread use, there were 14 severe anaphylactic reactions resulting in three deaths.

Anaphylactic reactions are rarely seen with the other antibiotics.

Serum sickness—The third major sensitivity complication of antibiotic therapy is "serum sickness." This does not differ in any respect from the classic form. That is, the reaction appears 8 to 12 days after administration of the drug and is characterized by fever, articular pains, dermal eruptions (usually urticaria) and lymphadenopathy. The constitutional reaction may be mild or severe, and symptoms may persist for many months. These reactions occur almost exclusively with penicillin.

Adelson[2] has remarked on the discovery of hypersensitivity in infants treated with penicillin. He found that if treatment is continued, vascular changes of the periarteritis nodosa type are produced. Walsh and Zimmerman[3]

examined the blood and bone marrow in six cases of serum sickness due to penicillin and found the L.E. factor in the plasma and L.E. cells in the bone marrow of the three patients with the most severe reactions. On the basis of these and other reports it seems probable that sensitivity reactions to the antibiotics may have a triggering effect in patients with a predisposition to collagen vascular disease.

Every physician who in the course of his practice utilizes antibiotics should be prepared to discover the patient with sensitization to antibiotics before using them and, if a reaction should occur, to recognize the reaction and treat it vigorously. He can do this with little extra effort, as he should always obtain a history of personal and familial allergy and specifically ask about reactions to previous antibiotic therapy. If there is any question, he should use another antibiotic or, if this cannot be done, accompany the administration with an antihistaminic or cortisone. We should keep in mind that many individuals who reacted once to an antibiotic may *not* react again.

Individuals who are sensitive to an antibiotic should carry identification noting their allergic history to the antibiotic.

The treatment of these reactions must, of course, be tailored to the individual reaction. In all cases, use of the antibiotic should be discontinued immediately. Mild reactions will respond to this measure alone, but an antihistaminic drug may be administered in therapeutic doses if deemed necessary. If the reaction is severe, 300 mg. of cortisone may be given in divided doses in the first 24 hours, with a gradual tapering off of the dose as improvement is noted, and meanwhile the antihistaminic drug is to be continued. Anaphylactic shock must be treated rapidly and vigorously with intravenous epinephrine, aminophylline and positive pressure oxygen.

It is also the duty of the physician to prevent sensitization. The cardinal guidepost in this is *not to use the antibiotics promiscuously.*

Several preparations of penicillin have appeared on the market which contain an antihistaminic. It is questionable and unlikely that concomitant administration of an antihistaminic will prevent delayed sensitization.

Metabolic alterations and vitamin deficiencies—The question frequently has been raised as to whether antibiotic therapy causes vitamin deficiencies. Much of this speculation has been prompted by the similarity of some of the oral and skin lesions caused by the antibiotics to those of vitamin deficiencies. Two mechanisms have been postulated by which this could happen: (1) The antibiotic may enter the biochemical cycles which involve vitamins and cause competitive inhibition, or (2) the bacteria in the bowel responsible for elaborating certain of the vitamins may be destroyed with consequent avitaminosis.

We have no specific evidence that either of these processes plays an appreciable role in antibiotic therapy in man.

When ordering antibiotics, the physician should consider their place in the total management of the patient. Oral antibiotics are adsorbed by aluminum hydroxide and therefore are of no benefit when it is also being administered. Friedman and associates[4] discovered that dihydrostreptomycin, TERRAMYCIN® and AUREOMYCIN® are inactivated by cation exchange resins. Not only is the patient who is receiving both by mouth deprived of the antibiotic effect, but the efficiency of the resins is also impaired. The diagnosis of jaundice can be confused by broad-spectrum antibiotic therapy. The organisms which alter the bile pigments in the intestine are suppressed; therefore, fecal and urinary urobilinogen may be absent.

3. Host Complications Incident to Responses of Microorganisms

Ecologic disturbances—From the beginning of antibiotic history it was noted that the ecology of the patient's flora was altered in the course of therapy. When penicillin was administered in lozenge form, the flora of the mouth was seen to change from a predominantly gram-positive to a predominantly gram-negative one. Opposite changes were observed in the flora of the bowel when streptomycin was given orally. From these early observations have emerged several clinical entities.

Staphylococcal diarrhea has recently been occupying the spotlight. This complication

may follow therapy with the broad-spectrum antibiotics, appearing about the fifth to twelfth day after treatment is initiated. About this time, due to changes in the intestinal flora, staphylococci become the predominant microorganism. What results is the same as a very severe episode of old-fashioned staphylococcal food poisoning, i.e., fever and diarrhea early in the course, and later dehydration, shock, oliguria and azotemia. Death, if it occurs, is due to toxemia, not septicemia. Dearing and Heilman[5] observed that this complication could be prevented if erythromycin is administered when staphylococci become the predominant organism in the stool. Cessation of therapy with the broad-spectrum antibiotics early enough may be adequate to prevent this.

A great variety of reactions have attended antibiotic therapy which have been attributed to fungous infections. Some of these are thrush, black hairy tongue, vaginitis, pruritus ani, proctitis, prolonged diarrhea and pulmonary disease. A diagnosis of moniliasis is usually made in such cases on the basis of smears or cultures from the lesions. Most of these are the result of topical use of antibiotics. Current opinion is that many of these lesions are wrongly attributed to fungous infections, the positive smears and cultures merely being a reflection of altered ecology common to patients receiving antibiotics, and not true infection.

Superinfection by a new organism in the course of treatment of another infection is not a rare phenomenon, if we are to judge by the number of reports in the journals. The majority of the reported cases arose in the course of penicillin treatment, and the organisms most often involved are *Hemophilus influenzae*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Serratia marcescens*.

The words "resistant organism" are familiar to every physician, yet there are many misconceptions associated with them. In short, the organisms which are most frequently troublesome because of resistance are the staphylococci, enterococci, *Proteus*, *pyocyaneus* and occasionally the coliform group. Frequently the organism is resistant to the antibiotic from the beginning. The only way to recognize this is to do adequate bacteriologic studies initially, use the indicated antibiotic and request sensitivity studies, if resistance is suspected or the infection is severe. Occasionally the organism is sensitive initially but becomes resistant in the course of treatment. The way to avoid this complication is to maintain a high index of suspicion and request sensitivity studies if the course of the disease does not go as expected. One should not scramble about switching frequently from one antibiotic to another hoping eventually to hit the right one. Resistance often is not an all-or-none phenomenon; sometimes merely increasing the dose of the antibiotic will bring the blood concentration to an effective level.

Recently we have all become aware of antibiotic antagonism, i.e., a "canceling-out" effect when certain antibiotics are used in combination. Although this phenomenon has been demonstrated experimentally in animals, it apparently is of limited importance clinically.

Summary

The highlights of the side effects due to antibiotic therapy have been discussed. Discrimination in the use of these potent agents should be practiced. Single antibiotics should be given whenever possible, based on definitive bacteriology and diagnosis. Doses should be adequate and therapy continued for an adequate period of time. Combinations of antibiotics should be used only where specifically indicated. Penicillin should not be given to patients in coma or to those unable to give an adequate history. Individuals allergic to the antibiotics should at all times carry identification indicating this.

REFERENCES

1. Kern, R. A. and Wimberley, N. A., Jr.: Penicillin reactions: Their nature, growing importance, recognition, management, and prevention. Am. J. M. Sc. 226:357 (October) 1953.
2. Adelson, L.: Periarteritis nodosa in infancy: Report of a case following allergic reactions to penicillin. J. Pediat. 39:346 (September) 1951.
3. Walsh, J. R. and Zimmerman, H. J.: Demonstration of L. E. phenomenon in patients with penicillin hypersensitivity. Blood 8:65 (January) 1953.
4. Friedman, I. S., Zuckerman, S. and McCatty, E.: Inactivation of antibiotics by cation exchange resins. Am. J. M. Sc. 225:399 (April) 1953.
5. Dearing, W. H. and Heilman, F. R.: Micrococcic enteritis as a complication of antibiotic therapy: Its response to erythromycin. Proc. Staff Meet., Mayo Clin. 28:121 (March 11) 1953.

Chlorpromazine and Reserpine in Psychiatric Practice

WINFRED OVERHOLSER*

George Washington University School of Medicine, and Saint Elizabeth's Hospital, Washington, D. C.

WINFRED OVERHOLSER

FROM time immemorial, various drugs have been used in the treatment of disturbed mental states. The particular drugs used have had their respective vogues, depending on the prevailing knowledge of pharmacology and on the rationale of their administration. In more recent years, there has been considerable reluctance to use sedative drugs because they were looked upon as merely substitutes for mechanical restraint, as something not therapeutic but merely palliative. Furthermore, such sedative drugs as paraldehyde, the barbiturates and chloral, if they quieted the disturbed patient, did so at the expense of impairing his consciousness and even of bringing about a stupor or deeper unconsciousness. Again, most of the sedatives used hitherto have been at least potentially toxic or addictive.

It is for these reasons that chlorpromazine and reserpine, which have recently become available in psychiatric practice, have attracted considerable attention. Both of them are relatively nontoxic; they have few or no side effects; there is a wide range of tolerance on the part of the patient, and there is virtually no impairment of consciousness, although a distinctly tranquilizing effect is noted from their use; furthermore, they are not addictive. It is thus not strange that the enthusiasm and the imagination of psychiatrists have been stirred.

Although these drugs have been available to American physicians only since 1953, many articles have been written on their use. Several of these are listed in the additional bibliography at the end of this article. These drugs are comparable in many ways, but there are differences in their actions and side effects. They, therefore, will be considered separately.

Chlorpromazine

This drug [10-(3-dimethylaminopropyl)-2-chlorphenothiazine]* is a derivative of phenothiazine. It originally was synthesized by the

*Department of Psychiatry, George Washington University School of Medicine and Saint Elizabeth's Hospital, Washington, D. C.

*Marketed as THORAZINE® by Smith, Kline and French Laboratories.

Poulenc Laboratories in France in 1952. It is administered in the form of the hydrochloride.

It apparently has a central depressant action on the reticular substance of the brain, combined with a powerful peripheral resistance to adrenalin. About 92 per cent of the drug is metabolized in the body. Among the side effects sometimes caused by the drug are hypotension, dryness of the mucosa of the nose and throat, occasional dizziness (possibly due to the hypotension), constipation and gastric hyperacidity, transitory fever, dermatitis of the erythema multiforme type, parkinsonian syndrome, agranulocytosis and jaundice. In the early stages of its administration there may be a certain amount of torpor or drowsiness. In cases in which either of these symptoms occurs, the electro-encephalogram is typical of normal sleep. A secretion of colostrum has occurred in a few cases in which the drug has been administered to female patients, but menstrual disturbances usually have not occurred. Photosensitivity of the skin is not uncommon during the administration of the drug.

It is in the mental sphere, however, that the particularly striking results of the drug have been noted. The drug first was used in preparing patients for operation and in treating hyperemesis of pregnancy, and it was observed that the patients exhibited a marked calmness and tranquility after the drug had been administered. This observation suggested that the drug possibly might be of value in psychiatric practice. It has been employed especially in the treatment of nervous tension, anxiety, assaultiveness, confusion, delirious and toxic psychosis such as alcoholic hallucinosis, and in the treatment of ambulatory schizophrenia, migraine and epilepsy. It occasionally has been helpful in cases in which depression has been associated with a considerable degree of tension and anxiety, but it is far more effective in the treatment of aggressive and assaultive behavior and tension. Motor unrest is diminished, anxiety is relieved, and the patient exhibits a general relaxation of mood.

The value of such a drug in institutional psychiatric practice can well be recognized. In view of its safety, it likewise is extremely valuable in private psychiatric practice. It has been reported that the drug has been used in more than 2.5 million cases and that fatal reactions have occurred in only three of the cases. In one case, death was due to liver damage; in two of the cases, it was due to agranulocytosis.

Dosage—The drug may be administered orally, intramuscularly or intravenously. Since a tolerance may be established rather easily, it is well to make sure that the initial dosage is adequate. This may be done effectively by administering 50 mg. of the drug intramuscularly on the first day, two doses of 50 mg. each on the second day, and three similar doses on the third day. On the fourth day, 300 mg. is administered orally, and the dose is increased thereafter as indicated. Ordinarily, a daily dose of 400 mg. is adequate, but in some cases it has been necessary to increase the dose to 900 mg. or more.

Side effects—As mentioned previously, the principal side effects, all of which apparently are reversible, are jaundice, fever and the parkinsonian syndrome. A very few instances of agranulocytosis have been reported. If urticaria or other skin symptoms develop, they respond promptly to administration of antihistamines, and all of the side effects disappear rather promptly after the administration of chlorpromazine is discontinued. Rarely, a "hibernation syndrome," characterized by lowered temperature, increased pulse rate, and miosis, is noted. Recovery occurs promptly if administration of the drug is discontinued. It has been observed that these side effects may not recur in cases in which the administration of the drug is resumed. Caution should be exercised in administering the drug in cases in which large amounts of the barbiturates have been used recently.

Results—The results in seriously disturbed mental patients in institutions often have been quite startling, and the drug has proved useful in office practice as well. The literature contains reports of cases of paranoid and catatonic schizophrenia in which patients who previously had been confused for considerable periods, hallucinated and aggressive in conduct appeared to exhibit logical thinking, increased

insight and improved judgment almost overnight after the drug had been administered for two or three weeks. Many patients of this type have been dismissed from the hospital and their improvement apparently has continued for a time, at least, after administration of the drug has been discontinued.

Improvement occurred in 85 per cent of 126 cases of catatonic or paranoid schizophrenia in which the drug was administered at St. Elizabeth's Hospital, but favorable results were not obtained in any cases of involutional depression or depression of the manic-depressive type.[1] Judging from this series of cases, it appears likely that the drug will produce improvement in 40 to 60 per cent of cases in which the patients have been in the hospital for five years or less and in at least 18 per cent of the cases in which the patients have been in the hospital for more than five years. The consensus appears to be that patients respond better to large doses of the drug than they do to small doses, and that treatment should be continued long enough for the maximal clinical response to occur.

Reserpine

This drug is an active alkaloid derived from the root of Rauwolfia serpentina.* It was isolated in 1952 in the laboratories of Ciba Pharmaceutical Products, Inc. It occasionally is supplied in combination with other sedatives.

Rauwolfia serpentina has been known for centuries in India, and it has been used in the Vedic system of medicine. It derived its name from Leonard Rauwolf, a German physician, who in 1582 published his botanical observations made in India and Africa. Shortly thereafter, this particular shrub was named in his honor.

There are many species of Rauwolfia. The shrub is widely distributed; it grows not only in India but also in Africa and South America. Before reserpine was isolated, the crude root was used medicinally for various purposes, such as treating snake bites and dysentery, and later in treating insomnia and mental disorders. Some less potent alkaloids had been isolated in 1931, and in 1933 some Indian writers noted that the root was a potent hypotensive agent. It was for this purpose that the drug first was introduced in the United States.

The effects of the drug most likely are due to an alteration of the parasympathetic balance by a partial suppression of the sympathetic predominance at the hypothalamic level. The general effects are sedation, reduced emotional response, peripheral autonomic alterations, and circulatory changes, especially in the nature of hypotension. The action of the drug is not especially rapid, and is somewhat cumulative. The drug is essentially nontoxic. The psychiatric indications for administration of the drug are similar to those for chlorpromazine, namely, conditions in which anxiety, tension, aggressiveness and excitement occur.

Dosage—This drug has a wide margin of safety, and the dosage is rather easy to adjust. The usual daily dose ranges from 0.1 to 1 mg. In a series of 108 cases in which the drug was used at St. Elizabeth's Hospital, the general plan was to begin treatment by administering 2 mg. daily by mouth or 2.5 mg. by the intramuscular route, and to increase the intramuscular dose by increments of 2.5 mg. until either a total dose of approximately 10 mg. was reached or until the desired tranquilizing effect was achieved.

Side effects—These are mild, and no serious toxic reactions have been reported. The patient may complain of lassitude or drowsiness until the dose is properly adjusted. Perhaps the most annoying symptom is dryness of the mucous membranes with "stuffiness" of the nasal mucosa.

Results—The results in the cases in which the drug was used at St. Elizabeth's Hospital have been summarized in part by Hoffman and Konchegul.[2] "For the 73 per cent who showed some degree of improvement the most common observations were a reduction of motor hyperactivity, of tension, of hostility and aggressiveness. Patients who had been untidy or careless in their dress now took more interest in their personal appearance. Communication with some of the patients became easier and their speech became more coherent

*Marketed as SERPASIL® by Ciba Pharmaceutical Products, Inc.; as SERPILOID® by Riker Laboratories, Inc. and as RAU-SED® by E. R. Squibb & Sons.

and less confused. They found it easier to talk about their delusions and hallucinations. While most, if not all, retained their abnormal content they seemed to be made less anxious by it. Sometimes, if they were willing to discuss their delusions or hallucinations at all, they gave the impression that their abnormal ideas were actually not their own but rather those of a third person."

Hoffman and Konchegul concluded (and their remarks are equally applicable to chlorpromazine), "The hypnotic drugs, as commonly used, made more definitive and lasting therapy impossible. This drug *demands* that every other therapeutic resource available be used intelligently in the further treatment of our patients, for the patients who respond to reserpine are now more accessible to such therapy. Rather than solving the difficult problems of the hospital treatment of the mentally ill, the availability of a drug such as this introduces grave problems for the conscientious hospital administrator, psychiatrist, and nurse. It will be found, we believe, that while the burdens of caring for the disturbed are lessened by reserpine, the challenge of providing appropriate additional psychiatric treatment for those no longer disturbed will tax all of our ingenuity, skill, and resources."

Conclusions

Chlorpromazine and reserpine appear to offer great possibilities, particularly in the institutional care of disturbed mental patients. They tranquilize without producing stupor, and make the patient not only more calm and less anxious but also clearer and more accessible for psychotherapy. It is altogether too early to say what the long-term results of the use of these drugs may be, and caution as to their possible untoward long-range effects should not be overlooked. Nevertheless, there is every reason to believe that they have marked a new era in the treatment of the mentally ill.

REFERENCES

1. Riesenman, F. R.: Preliminary Report on Thorazine Therapy on Women's Receiving Service, Saint Elizabeth's Hospital, Washington, D.C. Not published.
2. Hoffman, J. L. and Konchegul, L.: Clinical and psychological observations on psychiatric patients treated with reserpine. Ann. New York Acad. Sc. 61:144-149 (April 15) 1955. To be published.

ADDITIONAL BIBLIOGRAPHY

Chlorpromazine

Barsa, J. A. and Kline, N. S.: Combined reserpine-chlorpromazine therapy in disturbed psychotics: A preliminary report. Am. J. Psychiat. 111:780 (April) 1955.

Charatan, F. B. E.: Evaluation of chlorpromazine ("largactil") in psychiatry. J. Ment. Sc. 100:882 (October) 1954.

Editorial: Chlorpromazine. Lancet 2:637 (September 25) 1954.

Elkes, J. and Elkes, C.: Effect of chlorpromazine on the behavior of chronically overactive psychotic patients. Brit. M. J. 2:560 (September 4) 1954.

Goldman, D.: Treatmnt of psychotic states with chlorpromazine. J.A.M.A. 157:1274 (April 9) 1955.

Lehmann, H. E.: Therapeutic results with chlorpromazine (largactil) in psychiatric conditions. Canad. M. A. J. 72:91 (January 15) 1955.

Lehmann, H. E. and Hanrahan, G. E.: Chlorpromazine. Arch. Neurol. & Psychiat. 71:227 (February) 1954.

Winkelman, N. W.: Chlorpromazine in the treatment of neuropsychiatric disorders. J.A.M.A. 155:18 (May 1) 1954.

Reserpine

Barsa, J. A. and Kline, N. S.: Combined reserpine-chlorpromazine therapy in disturbed psychotics: A preliminary report. Am. J. Psychiat. 111:780 (April) 1955.

Dustan, H. P., Taylor, R. D., Corcoran, A. C. and Page, I. H.: Clinical experience with reserpine (Serpasil): A controlled study. Ann. New York Acad. Sc. 59:136 (April 30) 1954.

Freis, E. D. and Ari, R.: Clinical and experimental effects of reserpine in patients with essential hypertension. Ann. New York Acad. Sc. 59:45 (April 30) 1954.

Gaunt, R. and others: Endocrine aspects of the pharmacology of reserpine. Ann. New York Acad. Sc. 59:22 (April 30) 1954.

Greenblatt, R. B. Use of reserpine (Serpasil) in certain gynecologic disorders. Ann. New York Acad. Sc. 59:133 (April 30) 1954.

Hafkenschiel, J. H. and Sellers, A. M.: Intravenous reserpine in patients with essential hypertension. Ann. New York Acad. Sc. 59:54 (April 30) 1954.

Harris, R.: Clinical use of reserpine (Serpasil) in geriatrics. Ann. New York Acad. Sc. 59:95 (April 30) 1954.

Kline, N. S.: Use of *Rauwolfia serpentina* Benth. in neuropsychiatric conditions. Ann. New York Acad. Sc. 59:107 (April 30) 1954.

Moyer, J. H.: Cardiovascular and renal hemodynamic response to reserpine (Serpasil), and clinical results of using this agent for the treatment of hypertension. Ann. New York Acad. Sc. 59:82 (April 30) 1954.

Noce, R. H., Williams, D. B. and Rapaport, W.: Reserpine (Serpasil) in the management of the mentally ill and the mentally retarded. J.A.M.A. 156:821 (October 30) 1954.

Plummer, A. J. and others: Pharmacology of *Rauwolfia* alkaloids, including reserpine. Ann. New York Acad. Sc. 59:8 (April 30) 1954.

Schlitter, E. and others: Chemistry of *Rauwolfia* alkaloids, including reserpine. Ann. New York Acad. Sc. 59:1 (April 30) 1954.

Schneider, J. A. and Earl, A. F.: Effects of Serpasil on behavior and autonomic regulating mechanisms. Neurology 4:657 (September) 1954.

Wilkins, R. W.: Clinical usage of *Rauwolfia* alkaloids, including reserpine (Serpasil). Ann. New York Acad. Sc. 59:36 (April 30) 1954.

Winsor, T.: Human pharmacology of reserpine. Ann. New York Acad. Sc. 59:61 (April 30) 1954.

Significance of a Lump in the Parotid Gland

JOHN C. LUCAS,* WILLIAM NEWMAN AND CALVIN T. KLOPP

George Washington University School of Medicine, Washington, D. C.

JOHN C. LUCAS

WILLIAM NEWMAN

CALVIN T. KLOPP

If it is probable that a given lump may represent a curable cancer, and if this probability is greater than the risk of biopsy, this diagnostic procedure should be used. According to Hinton and Lord,[1] biopsy will disclose a malignant lesion in 6.7 per cent of cases of clinically benign lesions of the breast. Since the mortality rate of excision of a lump in the breast is far less than 1 per cent, a lump of this type always should be removed. These authors also reported that pathologic examination disclosed cancer of the thyroid gland in 7.6 per cent of 184 cases of clinically benign nodular goiter. Since the mortality rate of excision of a clinically benign solitary lump in the thyroid gland also is less than 1 per cent, the lump always should be removed. Similar reasoning ought to apply to masses occurring in other areas until such time as diagnostic acumen improves to the point where accurate distinction between benign and malignant tumors can be made by a nonsurgical test or, less probably, by clinical examination alone.

In cases in which a mass occurs in one of the salivary glands, the tendency unfortunately has been to "wait and see." This is illustrated by the following case report.

A 37 year old woman had noted a lump beneath the lobe of the left ear six months before she consulted a physician. Since the mass had been discovered accidentally, it is possible that it might have been present for several years. She had consulted one physician, who had not advised any treatment, an otolaryngologist, who had told her that it could be

Departments of Surgery and Pathology and the Cancer Clinic of the George Washington University School of Medicine, Washington, D. C.

*Trainee of the National Cancer Institute, Washington, D. C.

removed but did not advise its removal, and a gynecologist, who had referred her for definitive treatment.

Examination revealed a nodule about 1 cm. in diameter which was situated below the lobe of the left ear, apparently in the parotid gland. Excision of the mass was advised, but the patient decided to defer the operation for two months. Subsequent histologic examination revealed that the tumor was a highly malignant carcinoma. Total parotidectomy with sacrifice of the facial nerve was recommended, but the operation was refused. One year has elapsed since the mass was excised, and the tumor obviously has recurred locally.

This patient had been told to "wait and watch" the lump. When a diagnosis of cancer was made, she was quite upset and wondered why each of the reputable physicians previously seen should not have told her that the lump possibly might be a cancer.

It is the purpose of this paper to show that tumors of the parotid gland are more likely to be malignant than are tumors of the breast or thyroid gland. We believe that all persistent tumors of the parotid gland should be investigated by biopsy and that a definitive operation should be performed without delay. Many patients and, unfortunately, some physicians believe that partial or complete removal of the parotid gland is associated with a great risk of permanent disability. Experience proves that such risk is negligible.

Since it is not widely appreciated that a malignant lesion of the parotid gland may appear as an asymptomatic mass, we made a study of 50 consecutive cases in which the chief complaint was a lump or swelling apparently within the parotid gland. Each patient was examined by at least one of us. This series of cases represents in essence cases in which the patients might be expected to consult any physician for diagnosis and treatment. We hope that the results of this study will suggest that there is little purpose in "watching" lumps within or apparently within the parotid gland, and that such lumps should be surgically excised to establish an early and accurate diagnosis.

The term parotid cancer must be defined. In general, a cancer must be capable of metastasizing or of invading surrounding normal tissue. The most common parotid tumor is the mixed tumor. While many mixed tumors, if untreated, behave in a benign manner for many years, they may ultimately behave as malignant and invasive growths. Whether this indicates that they were actually torpid malignant tumors from their inception or that they have undergone malignant transformation is not germane to this discussion. The latter concept is usually accepted. Some pathologists distinguish benign from malignant mixed tumors. In this paper the term parotid cancer does not include benign mixed tumors.

The classification offered by Foote and Frazell[2] was used to classify the tumors in these cases (table 1). All of the available slides were reviewed by one of us who had trained at the Memorial Center in New York and who had had an opportunity to see much of the material that formed the basis for the paper by Foote and Frazell.[2] The use of this classification permits comparison with the much larger series of cases reported by these

TABLE 1

HISTOLOGIC CLASSIFICATION OF PAROTID TUMORS IN 50 CASES

HISTOLOGIC CLASSIFICATION	CASES	
	Number	*Per Cent*
Mixed tumors (32 cases; 64 per cent)		
Benign	24	48
Malignant	8	16
Carcinomas (11 cases; 22 per cent)		
Muco-epidermoid	6	12
Squamous	1	2
Adenoid cystic	2	4
Acinic cell adenocarcinoma	1	2
Miscellaneous types	1	2
Oxyphil adenoma	1	2
Benign lympho-epithelial lesion*	2	4
Unclassified		
Benign	1	2
Malignant	1	2
Chronic parotitis	2	4

*Lesion was the same as that described as Mikulicz's disease.[3-5]

authors. In our series, 20 (40 per cent) of the tumors were malignant and 30 (60 per cent) were benign.

The diagnosis of malignant mixed tumors is contingent on finding evidence of malignant cellular transformation or vascular or lymphatic permeation in addition to areas of clearly defined benign mixed tumor. It follows that an adequate number of sections (at least four), including the capsule, must be available for study. Our material includes fewer unclassified tumors than does that of Foote and Frazell[2] only because the aspiration biopsy technic so frequently employed for diagnosis at the Memorial Center was not used, and hence more tissue was always available for study.

Muco-epidermoid carcinomas are all considered malignant and are separated into low grade and high grade tumors. The adenoid cystic carcinomas and acinic cell adenocarcinomas[6] are separated from miscellaneous types of carcinoma because of their distinctive histologic appearance and somewhat better clinical documentation.

Since the patients in these cases had been operated on in several hospitals, different pathologists had examined the microscopic slides. When these slides were reclassified by one of us, neither the previous diagnosis nor the clinical course of the patient was known to him.

Originally, most of the mixed tumors were not classified as benign or malignant. In the present study, eight of these tumors were classified as malignant. Of the eight patients who had malignant tumors, only one is free of disease. This patient was operated on 18 months before this paper was written. Four of the patients are known to be dead, and one of the four probably died of the malignant tumor. Another patient has undergone a radical dissection of the neck for a recurrence of the tumor eight months after the initial operation. Ten months have elapsed since the last operation, and the patient does not have any evidence of the disease. The remaining patient is still living, but the tumor has recurred in the skin of the neck. In two of these eight cases, the tumors previously had been called benign. In one of these two cases, the patient died of metastatic lesions in the cervical lymph nodes, mediastinum and lungs soon after the operation. At autopsy, the lesion in this case still was classified as a mixed tumor.

The tumor has recurred in only one of the 24 cases in which the tumors were reclassified as benign mixed tumors. However, in the remaining 23 cases, operation was performed less than seven years ago, and in several cases it was performed only within the past year. In the case in which the tumor recurred, the patient had been operated on twice before. The first excision had been performed 12 years previously.

The preceding observations would suggest that a pathologist who sees a fair amount of salivary gland material can, with reasonable accuracy, separate benign from malignant mixed tumors, and, furthermore, that the histologic diagnosis is often an accurate parallel of the subsequent clinical course of the patients. The clinical experience reported includes cases of muco-epidermoid carcinomas. Frozen section diagnosis of parotid tumors in those instances in which multiple sections, including the capsule, are necessary for accuracy presents an obvious hazard of unnecessary operation. Except in those instances in which the tumor is obviously malignant, we prefer to wait for the preparation of permanent paraffin sections.

Clinical Features

In our series of 50 cases, the clinical features were similar to those in the cases reported by other authors and recently summarized by Frazell.[7] Of the 50 patients, 33 were females and 17 were males. Average age of the patients with benign tumors was 39.4 years, and that of the patients with malignant tumors was 50.3 years. The most common symptom was a slowly growing, painless mass in the vicinity of the lobe of either ear. Eight (16 per cent) of the patients complained of pain or discomfort. Of these eight patients, three had a carcinoma, two had parotitis and three had benign tumors. The tumors had been present on an average of 42 months. However, those tumors considered histologi-

cally to be highly malignant had been present on an average of only one and a half years.

Surgical Complications

Facial paralysis—Since it is possible to remove the entire superficial lobe of the parotid gland without causing permanent injury of the facial nerve, permanent paralysis of the facial nerve rarely should occur after excision of a parotid tumor which does not involve this nerve. Excision should be distinguished from enucleation. The latter procedure is not considered proper treatment, and it probably is responsible for the high rate of recurrence in reported cases of parotid tumors.

According to Marshall,[8] the reported incidence of injury of the facial nerve in the course of operations on the parotid gland varies between 4.4 and 16.9 per cent. In some of the reported cases, the nerve was injured deliberately in order to remove a malignant tumor. The entire facial nerve was deliberately sacrificed in six of the cases in our series, the lower half of the nerve was destroyed in one case, and a small mandibular branch was destroyed in another case. In all of these eight cases, the parotid tumor was malignant. Permanent paralysis of the facial nerve did not occur in any of the cases in which operation was performed to secure a biopsic specimen or to remove a benign tumor. It should be emphasized that transient facial paralysis commonly occurred in the first two months after operation.

Auriculotemporal syndrome—In one case, an auriculotemporal syndrome[9] developed after the superficial lobe of the parotid gland had been removed completely.

Salivary fistula—A salivary fistula has developed in one case and has persisted for 18 months. The patient has refused to have the fistula repaired.

Summary

This paper is based on a study of 50 consecutive cases in which the chief complaint was a lump or swelling in the parotid gland. In 20 (40 per cent) of the cases, the lump was found to be malignant.

In cases in which a lump is present in the parotid gland, surgical biopsy can be performed with almost no danger of permanent injury of the facial nerve or any other complications. The histologic appearance of parotid tumors can be accurately correlated with their biologic and clinical behavior. The "watch and wait" policy should not be followed in cases in which a lump is present in the parotid gland.

REFERENCES

1. Hinton, J. W. and Lord, J. W., Jr.: Is surgery indicated in all cases of nodular goiter, toxic and nontoxic? J.A.M.A. 129:605 (October 27) 1945.
2. Foote, F. W., Jr. and Frazell, E. L.: Tumors of the major salivary glands. Cancer 6:1065 (November) 1953.
3. Godwin, J. T.: Benign lympho-epithelial lesion of parotid gland. Cancer 5:1089 (November) 1952.
4. Morgan, W. S. and Costleman, B.: Clinicopathologic study of Mikulicz's disease. Am. J. Path. 29:471 (May-June) 1953.
5. Morgan, W. S.: Mikulicz's disease and Sjögren's syndrome. New England J. Med. 251:5 (July 1) 1954.
6. Godwin, J. T., Foote, F. W., Jr. and Frazell, E. L.: Acinic cell adenocarcinoma of the parotid gland. Am. J. Path. 30:465 (May-June) 1954.
7. Frazell, E. L.: Clinical aspects of tumors of the major salivary glands. Cancer 7:637 (July) 1954.
8. Marshall, S. F. and Miles, G. O.: Tumors of submaxillary and parotid gland areas. S. Clin. North America 27:501-516 (June) 1947.
9. Bassae, P.: Auriculotemporal syndrome. M. Clin. North America 16:405 (September) 1932.

41st International Postgraduate Medical Assembly

a distinctive meeting of

CLINICS, LECTURES and PANELS

• • •

Cleveland, Ohio — October 22-23-24-25, 1956

Fractures of the Nose

MAXINE SCHURTER AND GORDON S. LETTERMAN*

George Washington University School of Medicine, Washington, D. C.

THE position and prominence of the nose make it highly susceptible to injury. As a result, the incidence of nasal bone fractures is exceedingly high. Further, due to the position of the nose on the face, these fractures may produce such physiologic and cosmetic disabilities as to result in definite economic and psychic hazards. To minimize these disabilities, treatment must be both adequate and early. Adequacy of treatment depends to a large extent on a clear understanding of the surgical pathology. Delay in instituting treatment may necessitate extensive late surgical procedures and should be avoided, unless associated intracranial, thoracic or abdominal injuries make early treatment impractical.

MAXINE SCHURTER

GORDON S. LETTERMAN

Anatomy

The framework of the external nose is composed of bones and cartilages (figure 1). The nasal bones form the bridge of the nose and articulate above with the frontal bones, laterally with the frontal processes of the maxillae, medially with each other, and inferiorly with the upper lateral cartilages. They are attached in the midline to the perpendicular plate of the ethmoid bone and the septal cartilage. The cartilaginous septum articulates with the perpendicular plate of the ethmoid, the vomer, the nasal spine of the maxilla, the nasal bones and the upper lateral cartilages.

Surgical Pathology

The deformity after injury varies with the mass and shape of the traumatizing object and with the force and site of the impact. Displacement and impaction or comminution generally

*Department of Surgery, George Washington University School of Medicine, Washington, D. C.

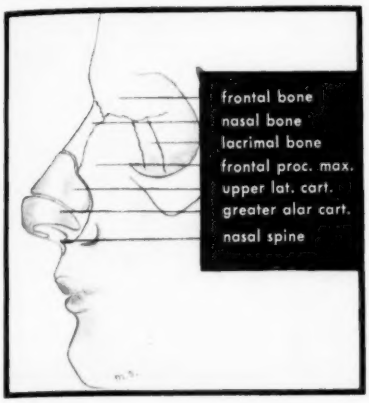


FIGURE 1. Anatomy of the external nose.

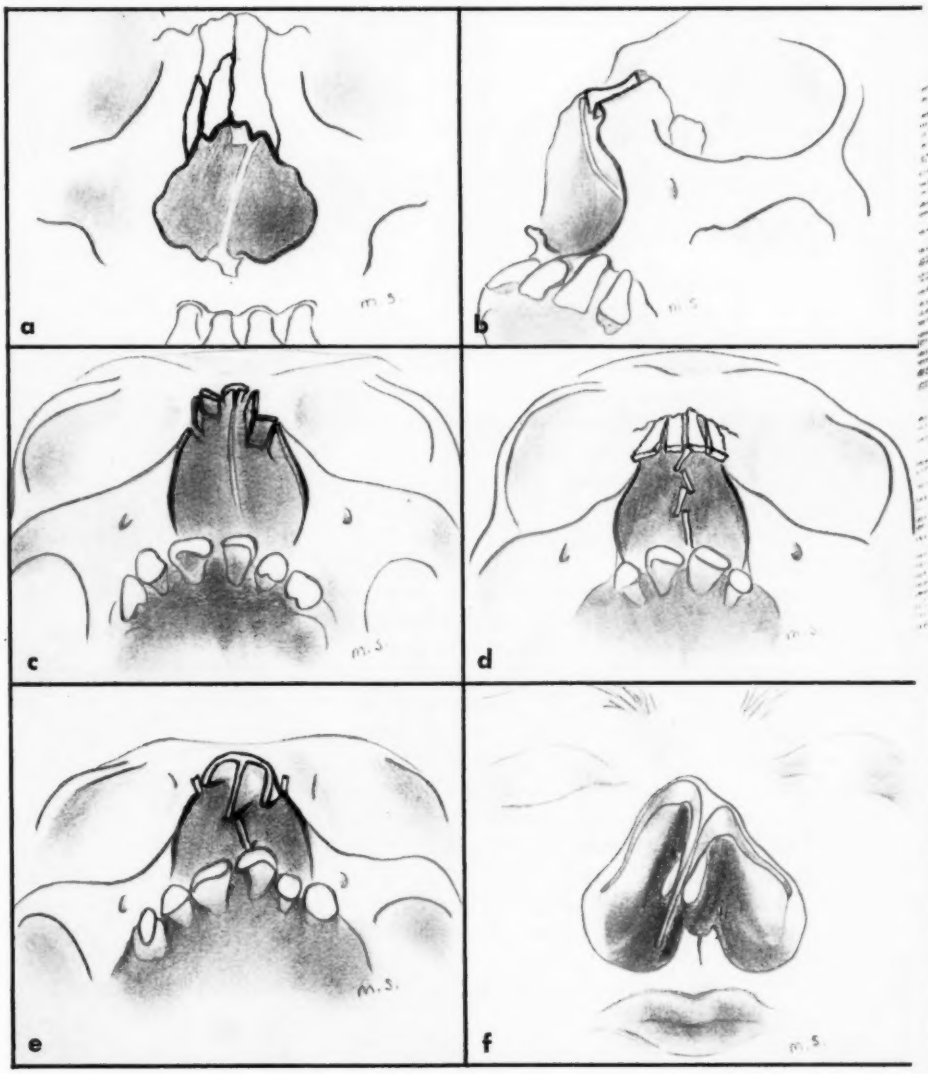


FIGURE 2a. Nasal bone fracture without displacement.

b. Unilateral depressed fracture.

c. Lateral displacement of the nose.

d and e. Saddle nose or depressed bridge.

f. Dislocated septum.

FIGURE 3a. Transverse fracture of the maxilla with nose driven inward.

b. Reduction of fracture shown in "a," with intranasal splint.

result from forceful contact with objects having flat surfaces and considerable weight. Lines of displacement are determined by the direction of the force, and the degree of displacement is proportional to the amount of the force. Bone or cartilage is susceptible to either fracture or displacement or to both.

A lateral blow to the bridge of the nose may result in a fracture of the nasal bones and frontal processes of one or both sides. Depending on the nature of the blow, therefore, there may be no displacement (figure 2a), a depression on one side (figure 2b) or a depression on one side with elevation on the opposite side (figure 2c).

A direct blow to the front of the nose may cause a bilateral nasal bone fracture with a saddle-nose deformity (figure 2d, e). The septal cartilage may be dislocated from its groove in the vomer, having slipped off to one side and causing a deviation and depression of the dorsum (figure 2f).

A blow to the tip of the nose may result in a fracture of the nasal spine of the maxilla, a vertical or horizontal fracture of the septal cartilage or displacement of the septal cartilage back against the perpendicular plate of the ethmoid.

In a crushing injury, the entire nasal structure may be driven inward with detachment from the frontal bones above and maxillary bones laterally, allowing the septum to be pushed into the ethmoid. This may occur in a transverse fracture of the maxilla (figure 3).

Occasionally, the nasolacrimal apparatus is injured in fractures of the nose because of its proximity to the frontal process of the maxilla. The chief physical finding in this instance is epiphora. The lacerated duct frequently can be repaired over fine polyethylene tubing. If the distal end cannot be secured, a new canal will form around polyethylene tubing which is brought out through nasal mucosa near the inferior turbinate.

Diagnosis

Lateral, Waters and Caldwell are the three roentgenographic views usually employed for examination of the bony structures (figures 4 to 6). Cartilaginous nasal structures, however, can be demonstrated only by specialized soft-tissue technics. Careful inspection and palpation have been found to be more effective in evaluating nasal injuries than any other diagnostic aids.

Fracture of the nasal bones causes marked ecchymosis and edema around the bridge, root

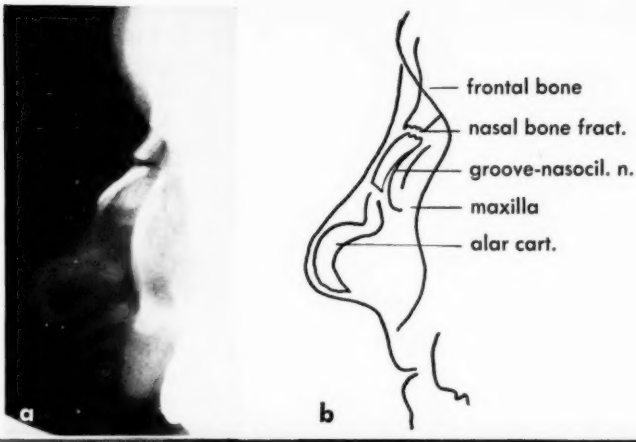


FIGURE 4. Lateral x-ray and diagram showing nasal bone fracture.

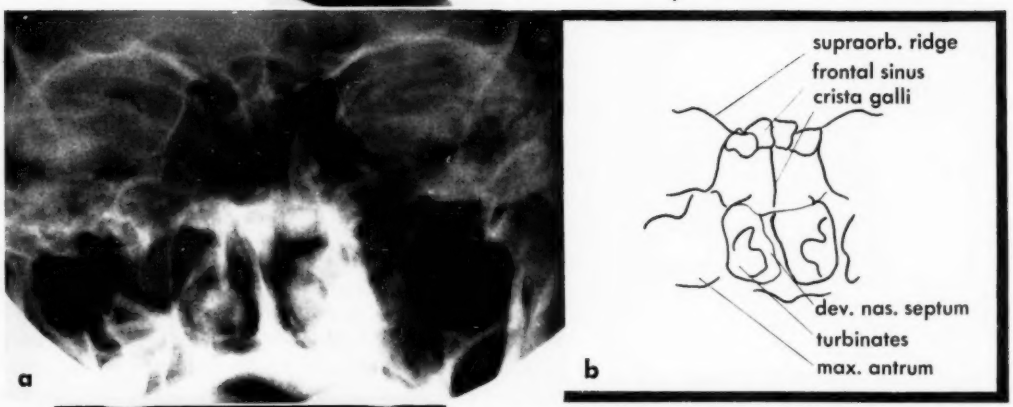


FIGURE 5. Caldwell view and diagram.

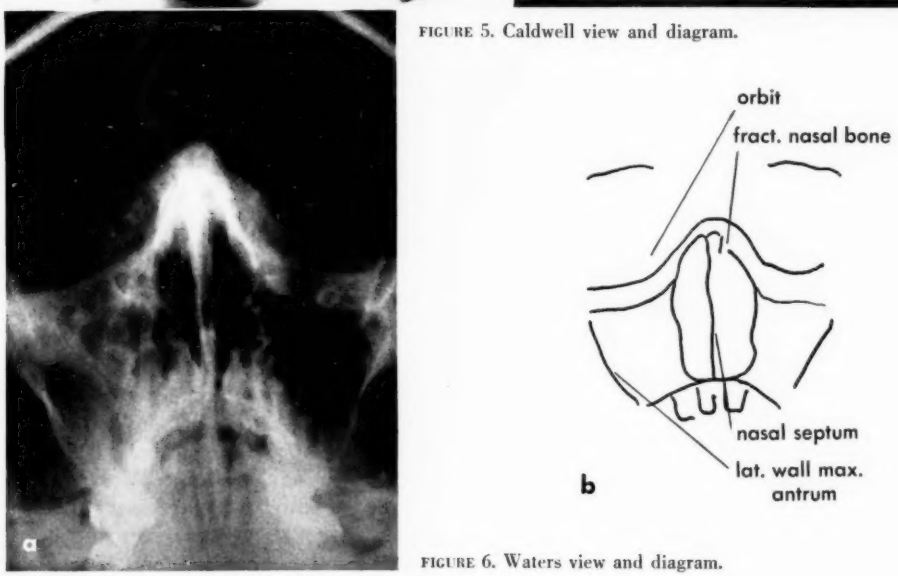


FIGURE 6. Waters view and diagram.

FIGURE 7a. Depressed bridge due to old fracture.

b. After cartilage implant.

and orbit. The presence of epistaxis is an excellent indication that the nasal mucosa has been torn by a fragment of bone or cartilage.

Depressions and irregularities of the framework are revealed by light palpation. If the nasal spine has been fractured, crepitation and tenderness will be felt on palpating the area between the upper lip and columella. Deviations of the cartilaginous septum and occlusion of the airways are determined by visualizing the nasal passages with a speculum.

Anesthesia

The anesthesia required for reduction of a nasal fracture ranges from none to oral endotracheal, depending on the severity of the injury and on the type and age of the patient. Local anesthesia may be obtained by inserting 5 to 20 per cent cocaine sponges. This may be supplemented, if necessary, by blocking the infra-orbital nerves, the nasociliary nerve and the columella with procaine or XYLOCAINE®.

Treatment

General—As previously stated, nasal fractures should be reduced early unless such reduction is contraindicated by associated injuries. Where delay is necessary, adequate reduction can be achieved with little difficulty within six or seven days after injury.

Technic—Treatment varies with the type of injury sustained. Epistaxis may be controlled by packing the nasal passages with weak ADRENALIN®-soaked sponges, and congestion lessened with 0.25 per cent NEO-SYNEPHRINE® packs. Where no displacement of the fractured fragment is evident, splinting to prevent further injury has been found to be adequate.

Unilateral depressions are reduced easily by inserting a suction tip or the broad, flat end of a knife handle up under the fragments and pushing outward, using the maxilla below as a fulcrum. In bilateral fragmentation, one blade of a rubber-shod Kelly clamp is inserted into each nostril to elevate the bones. At the same time, the fingers of the free hand are placed on the outside of the nose and the pieces molded into proper position. This method also applies to saddle-nose fractures. With reduction of the bones the septum and alar cartilages usually fall into place. Manipulation of the septum may be necessary if it has been dislocated from its groove in the vomer. Forward traction is needed to effect replacement.

Where both nasal bones and septum have been broken, the fragments may be difficult to hold in place. In such instances a through-and-through wire sling may be applied to hold the nose forward. Two No. 24 stainless steel wires are passed through each frontal process with the septum between and tied on either side of the nose over small lead plates used to protect the skin. Where the entire nose is driven inward, as in a transverse maxillary fracture, it may be necessary to hold the bone forward by an intranasal splint attached to a plaster head bandage (figure 3b).

Postoperative treatment—After reduction, the nasal passages are packed lightly with VASELINE® gauze for immobilization and control of epistaxis. An aluminum or dental wax splint is then applied and taped to the face for protection from further injury. The Vaseline gauze may be removed in three to four days and the splint in 7 to 10 days.

Correction of Late Deformities

Inadequately treated nasal fractures result in a number of unpleasant sequelae including the saddle-shaped and crooked nose. Further, the nasal passages may be narrowed, causing not only difficulty in breathing but also sinusitis with all its symptoms. Treatment of these late deformities consists of a submucous resection with septal reconstruction for deviated septum, rhinoplasty for the crooked nose, and cartilage or bone transplants to elevate the dorsum of a depressed bridge or saddle nose (figure 7).

Summary

Treatment of nasal bone fractures must be adequate and early to obtain satisfactory results. A clear understanding of the injury in relation to the normal anatomy of the nose is basic to administering proper treatment.

Since the pathology varies with the nature of the blow, information on the latter aids in diagnosis. In general, palpation has been found to be the best means of diagnosis. Technics of treatment are based on type of injury. Reconstruction of the nose can be used to correct late deformities.

REFERENCES

1. McDowell, F., Brown, J. B. and Fryer, M. P.: Surgery of Face, Mouth, and Jaws. St. Louis, The C. V. Mosby Company, 1954.
2. Brown, J. B. and McDowell, F.: Plastic Surgery of the Nose. St. Louis, The C. V. Mosby Company, 1951.
3. Kazanjian, V. H. and Converse, J. M.: The Surgical Treatment of Facial Injuries. Baltimore, Williams and Wilkins Company, 1949.

Make Plans Now to Attend

The Forty-First Annual Assembly

of the Interstate Postgraduate Medical Association of North America

• • •

to be held in Cleveland, Ohio

October 22-25, 1956

Local Anesthesia

CHARLES S. COAKLEY*

George Washington University School of Medicine, Washington, D. C.

ALMOST any surgical procedure can be accomplished under local anesthesia. The requirements for successful local anesthesia are knowledge of anatomy, technic of the block, and pharmacology of the local anesthetic drugs.

CHARLES S. COAKLEY

Local anesthesia is the term most often used for all types of regional anesthesia. Local anesthesia may be classified as topical anesthesia, infiltration anesthesia, field blocks and nerve blocks.

Topical anesthesia is produced by anesthetizing the body surfaces, infiltration anesthesia by injecting an anesthetic into tissues of the surgical site, field blocks by walling off the operative site, and nerve blocks by more accurately injecting an anesthetic into the vicinity of nerves.

*Department of Anesthesiology, George Washington University School of Medicine, Washington, D. C.

The indications for the use of local anesthesia for major operations have been reduced owing to improvements in general anesthesia and the intravenous use of anesthetic drugs. However, there is a place for local anesthesia in surgical practice. One example is in cases in which minor surgical procedures are to be performed on ambulatory patients. This paper will be limited to this aspect of local anesthesia.

The landmarks in the history of local anesthesia have been the discovery of cocaine by Niemann in 1860, the first clinical use of cocaine by Koller in 1884, the synthesis of procaine by Einhorn in 1905, and the publication of "Regional Anesthesia" by Labat in 1922.

A thorough knowledge of anatomy is essential for field and nerve blocks, but not for topical and infiltration anesthesia. Osteology must be understood so that bony prominences can be used as landmarks to locate the nerves. Also, the relationship of these nerves to large blood vessels must be known.

The physician who uses local anesthetic

procedures should be thoroughly familiar with the technical aspects of the block. He should be gentle and should maintain a constant physician-patient relationship. It is necessary to use an aseptic technic for all nerve blocks. The technic of these local anesthetic procedures is available in recent books[1-5] and will not be discussed in this paper.

The local anesthetic reactions and complications should be familiar to anyone using local anesthesia. Since the synthesis of procaine in 1905, many local anesthetic drugs have been developed. However, procaine hydrochloride (NOVOCAIN®), milligram for milligram, still is the least toxic of all of these drugs. Tetracaine hydrochloride (PONTOCAINE® hydrochloride) is more toxic than procaine hydrochloride but it is effective when administered in solutions one-tenth as strong as effective solutions of the latter drug. Thus tetracaine hydrochloride is relatively less toxic than procaine hydrochloride.[6,7] It has the advantage of producing anesthesia of longer duration than that produced by procaine, but it has the disadvantage that the anesthesia is of slower onset.

Other local anesthetic drugs that are being used include piperocaine hydrochloride (METYCAINE® hydrochloride), hexylcaine hydrochloride (CYCLAINE® hydrochloride) and lidocaine hydrochloride (XYLOCAINE® hydrochloride).[8,9] Piperocaine hydrochloride is slightly more toxic than procaine hydrochloride but its action is more prolonged. The effect of lidocaine hydrochloride lasts as long as that of piperocaine hydrochloride, but the action of this drug is more rapid than that of piperocaine hydrochloride. It has been our experience that it is more toxic than procaine hydrochloride. Toxic reactions to this drug are manifested by drowsiness and hypotension. Since doses exceeding 350 mg. (35 cc. of a 1 per cent solution) frequently produce these reactions, we do not inject more than this amount at one time.

The most common error in the use of local anesthesia is not allowing sufficient time for the development of anesthesia after the anesthetic agent has been injected. The time interval necessary for the onset of anesthesia must be known for the particular anesthetic drug being used.

Precautions should be taken to prevent toxic reactions and complications in cases in which local anesthesia is used.[10] Toxic reactions can be prevented by taking a careful history to determine whether the patient has had a previous anesthetic reaction, by using the smallest volume of the anesthetic solution and the lowest concentration of the anesthetic agent that will produce satisfactory anesthesia, by avoiding intravascular injection, and by checking the drug label and the drug concentration in each case.

Toxic reactions cause a stimulation of the central nervous system and the cardiovascular system which is followed by a depression. Restlessness, tremors, convulsions, and an increase in the pulse rate, respiratory rate and blood pressure occur and are followed by a decrease in the blood pressure, pulse rate and respiratory rate.

Treatment of these reactions consists of the intravenous administration of an ultrashort-acting barbiturate to control the convulsions, the intravenous administration of fluids and vasopressor drugs, if necessary, to control the low blood pressure, and the use of artificial respiration to control the respiratory depression. Tachycardia and increased blood pressure resulting from overdoses of vasopressor drugs usually are of short duration, but, if severe, can be controlled by administering a vasodilator. The administration of chlorpromazine perhaps may be of value in the treatment of this type of hypertension.

Allergic reactions are manifested by urticaria, angioneurotic edema and the more severe anaphylactic shock. These manifestations usually can be relieved by the administration of epinephrine or an antihistamine.

Any physician who is using local anesthesia should have resuscitation equipment and oxygen, a barbiturate, a vasopressor and an antihistamine available so that toxic reactions can be treated immediately.

Complications may result from local anesthesia. Adriani and Evangelou[11] reported that complications occurred in 12 (0.85 per cent) of 1400 instances in which regional anesthesia

was used. Thus, the incidence of complications other than drug reactions is low. Some of the complications that may occur in cases in which local anesthesia is used on ambulatory patients are syncope, psychogenic reactions, and hematomas, soreness or infection at the site of the injection. The signs and symptoms of syncope, which include pallor, sweating, nausea, vomiting, a slow pulse rate and a fall in the blood pressure, must be distinguished from those of a drug reaction. Treatment consists of lowering the patient's head, administering aromatic spirits of ammonia, and, in cases in which the complication is severe, administering a vasopressor or giving oxygen by inhalation method.

Toxic reactions have occurred in cases in which tetracaine hydrochloride and cocaine have been used for topical anesthesia.[12] The concentration of these anesthetics in solution and the volume of the solution must be kept minimal. When topical anesthesia is used for bronchoscopy, caution should be used to prevent the patient from swallowing the drug. We have used a 2 per cent solution of lidocaine hydrochloride for topical anesthesia for the past two years. It has not caused any toxic reactions, and it has produced satisfactory anesthesia.

Epinephrine is added to local anesthetic solutions to prolong the duration of anesthesia, to decrease the toxic effects, and to decrease the vascularity of the operative area. Systemic reaction consisting of increased pulse rate and elevated blood pressure may be caused by overdoses of epinephrine. A concentration of 1:200,000 is generally used. This is prepared by adding 0.5 cc. of a 1:1000 solution of epinephrine to 100 cc. of the local anesthesia solution. Concentrations as high as 1:50,000 are used in oral surgery. It is generally accepted that a total dose of 0.2 mg. of epinephrine can be safely administered to any patient with diseases of the heart and circulatory system.[13]

Summary

Local anesthesia for minor surgery on ambulatory patients is an indicated and widely used procedure. In using local anesthesia, the physician should have a working knowledge of anatomy, be familiar with the technic, and have a thorough understanding of the pharmacology of the drugs being used. He should be prepared to recognize and treat toxic and allergic reactions and any other complications that may arise.

REFERENCES

1. Southworth, J. L. and Hingson, R. A.: Conduction Anesthesia; Clinical Studies of G. P. Pitkin. Philadelphia, J. B. Lippincott Company, 1946.
2. Moore, D. C.: Regional Blocks; A Handbook for Use in Clinical Practice and Surgery. Springfield, Illinois, Charles C Thomas, 1953.
3. Lundy, J. L.: Clinical Anesthesia. Philadelphia, W. B. Saunders Company, 1942.
4. Adriani, J.: Nerve Blocks; A Manual of Regional Anesthesia for Practitioners of Medicine. Springfield, Illinois, Charles C Thomas, 1954.
5. Labat, G.: Regional Anesthesia. Philadelphia, W. B. Saunders Company, 1928, ed. 2.
6. Moore, D. C.: Use of Pontocaine hydrochloride for nerve block and infiltration analgesia, therapeutic and diagnostic blocks: 1004 cases. Anesthesiology 11:65 (January) 1950.
7. Nowak, S., cited by Saklad, M.: Spinal anesthesia; agents, methods and indications. New England J. Med. 213:1226 (December 19) 1935.
8. Gordh, T.: Kliniska erfarenheter med Xylocaine—ett nytt lokalanestikum. Svenska läk.-tidning. 45-116 (January) 1948.
9. Hanson, I. R. and Hingson, R. A.: Use of Xylocaine, new local anesthetic, in surgery, obstetrics and therapeutics; preliminary report. Anesth. & Analg. 29:136 (May-June) 1950.
10. A. M. A. Fundamentals of Anesthesia. Philadelphia, W. B. Saunders Company, 1954.
11. Adriani, J. and Evangelou, M.: Complications of regional anesthesia. Anesth. & Analg. 34:96 (March-April) 1955.
12. Weisel, W. and Tella, R. A.: Reaction to tetracaine (Pontocaine) used as topical anesthetic in bronchoscopy; study of 1000 cases. J.A.M.A. 147:218 (September 15) 1951.
13. New York Heart Association: Report to the Council of the New York Institute of Clinical Oral Pathology, 1954.

The Negative Myelogram and Nucleography

HENRY L. FEFFER* AND HUGO V. RIZZOLI†

George Washington University School of Medicine, Washington, D. C.

DANDY[1] in 1919 first used air to visualize the cerebral ventricles and the subarachnoid space roentgenographically. Though he was primarily interested in visualizing the brain, he predicted the use of air in the localizing intraspinal tumors. Wideröe[2] in 1921, using this technic, first reported the roentgen visualization of an intraspinal tumor in the cervical region. In 1925, Dandy[3] reported 10 cases of spinal cord tumors which were localized by air myelography.

HENRY L. FEFFER

HUGO V. RIZZOLI

Camp,[4] in an excellent review of contrast myelography, published in 1950, reported that Sicard and Forestier[5] in 1922 first used iodized oil (LIPIODOL®) as a contrast roentgenographic medium. They apparently had been injecting iodized oil extradurally in the lumbosacral area for the treatment of sciatica, when by accident some of the oil was introduced into the subarachnoid space. Subsequently, in 1929, Odin, Runström and Lindblom[6] reported undesirable meningeal reactions from the use of iodized oil. THOROTRAST® (thorium dioxide) was introduced for myelography by Radovici and Meller[7] in 1932. It never became a popular medium because it resulted in frequent untoward reactions and was not easily absorbed.

Widespread interest in myelographic diagnosis of herniated intervertebral disks was

*Department of Orthopedic Surgery; †Department of Neurosurgery, George Washington University School of Medicine, Washington, D. C.

stimulated by the clinical contribution of Mixter and Barr[8] in 1934 and the myelographic contribution of Hampton and Robinson[9] in 1936. Lipiodol was the medium most frequently used but renewed interest in air myelography was stimulated. In 1941, methods for aspirating the Lipiodol from the subarachnoid space after myelography were reported by Woodhall[10] and by Kubik and Hampton.[11]

In 1944, when Ramsey, French and Strain[12] introduced PANTOPAQUE® (ethyl iodophenylundecylate) as a nonirritating, absorbable medium, myelography became more widely accepted. Pantopaque was found to be much more easily removed, and although irritative effects have been described, the question remains as to whether these are due to rare individual hypersensitivity reactions, to the presence of bleeding, or possibly to contamination. Certainly Pantopaque has proved to be less irritating than Lipiodol. However, its slow rate of absorption has been disappointing. Pantopaque myelography has been accepted in most neurosurgical clinics as a relatively safe procedure provided that certain standards in technic are observed. No doubt the search will continue for a more perfect medium.

In Europe, Pantopaque has not been accepted with as much enthusiasm. Instead, 20 per cent abrodil (SKIODAN®) is used. Arnell and Lidström[13] in 1931 first reported the use of this substance, a water-soluble radiopaque medium which is quickly absorbed. Arnell's subsequent publications in 1944 and 1948[14,15] are responsible for popularizing this substance. However, abrodil requires the use of a spinal anesthetic and has not proved to be entirely without risk, for serious complications have occurred.[15]

Though the search for a more perfect opaque medium must continue, even the most ideal substance will leave much to be desired in the roentgenographic diagnosis of ruptured intervertebral disks. Subarachnoid myelography will never prove to be anything but a helpful aid of secondary importance as compared with a careful clinical evaluation. Regardless of the medium used, even large herniated disks will not be disclosed by this method of visualization if the caudal sac is too narrow or if it does not extend well below the fifth lumbar disk. Visualization will be impossible also if the disk protrusion is so far lateral that it does not indent the dural sac or produce a definite nerve root asymmetry.

If one interprets a myelogram objectively, without giving thought to the clinical picture, and considers positive only those cases in which a definite defect in the dural sac is visualized, 60 to 65 per cent of clinically significant ruptured intervertebral disks will be discovered. But, if one interprets the myelogram with the whole clinical picture in mind and considers mild nerve root asymmetries as suggestive of herniated intervertebral disks, this test will prove to be much more reliable. Rees and Donley[16] reported 86.8 per cent reliability in diagnosis of ruptured intervertebral disks, and stated that negative myelography is unreliable if the caudal sac is narrow. Scoville et al.[17] in 1948 reported from 25 to 35 per cent over-all error in 200 operative cases which had had Pantopaque myelography. Raaf and Berglund[18] in 1949 reported that, at surgery, Pantopaque myelography had proved only 76.7 per cent accurate. This test is useful in diagnosis of herniated intervertebral disk; however, its inaccuracy has stimulated the development of a more direct visualization of the disk itself.

Although it was in 1948 that Lindblom[19,20] of Sweden published the first account of the use of nucleography in detecting intervertebral disk degeneration, universal acceptance has been slow. Technical difficulty as well as an inherent fear of insidious complications have relegated disk puncture well behind myelography and even surgical exploration in importance as a diagnostic and localizing procedure.

Initial attempts at nucleography can be discouraging, and failures are common; however, we have been able to eliminate inadequacies in technic to the point where visualization has been successful in all of the last 30 patients examined. The average time required now compares favorably with that necessary for a myelogram.

The method used is a modification of that

described by Erlacher.[21] A routine sterile preparation of the lumbosacral region is performed and the area draped off with sterile towels after the patient has been flexed on his side and centered on the x-ray table for a lateral roentgenogram. The disk under investigation is punctured by inserting a 4 in., 22 gauge regional block needle through an anesthesized area 1.5 cm. lateral to the upper margin of the spinous process immediately below. A maximum interlaminar aperture and latitude in needle direction are afforded by directing the needle slightly upward and medially even when the lumbosacral disk is to be studied. The interspace thus is entered obliquely just over the superior margin of the inferior vertebra. Entrance into the annulus fibrosus is accompanied by a sensation of rubbery resistance, and the needle is then inserted about 1 cm. further.

It is difficult to remain outside the dura in every instance; however, the closer to the facet the ligamentum flavum is penetrated, the less the possibility of a transdural course and postspinal headache. The two lower disks are punctured routinely unless there is a definite reason for incriminating one at a higher level. With the needles in place, a lateral roentgenogram is taken and the accuracy of the position verified. A 35 per cent solution of iodopyracet (DIODRAST®) is injected into each under moderate pressure and the needles are withdrawn. Note is made of the amount of dye used as well as the patient's discomfort during the instillation at each level. Anteroposterior and lateral roentgenograms are taken immediately.

A degenerated disk demonstrates a diffuse spread of the dye throughout the interspace with or without a visible protrusion. Occasionally a distinct breach in the posterior annulus fibrosus is visualized by a free flow of the dye into the extradural space. The pathologic disk has a capacity of more than 1 cc., and a definite reproduction of the pain occurs at the time of injection. A normal disk usually accommodates 0.25 to 0.5 cc., and no significant discomfort is experienced by the injection. The roentgenogram in this shows a symmetrical, central, globular or bilocular pattern.

Complications of the procedure to date have been limited to mild headache in 15 of the 60 patients examined. Gardner and co-workers[22] have made an excellent review of the literature which contained 58 case reports implicating lumbar punctures as the cause of pathologic changes in intervertebral disks. Their analysis suggests that sepsis was introduced in most, and that this rather than simple trauma was responsible for resultant morbidity. They reported one such interspace infection out of a series of 89 patients examined nucleographically. It was difficult for them, as well as for us, to involve the trauma of disk puncture as the etiologic agent of subsequent destructive change. During surgical exploration it is common practice to check the capacity of a suspicious disk by injecting it with saline solution. Under direct vision we have never seen the slightest disruption in the continuity of the annulus fibrosus from needle puncture.

Neither the absolute nor the relative accuracy rates of myelography and nucleography ever have been scientifically evaluated. The percentage of false positive myelograms can easily be determined surgically; however, the number of false negatives is obscure. The patients continue under conservative management and are explored only when completely incapacitated. The evidence furnished by the nucleogram is less circumstantial and more direct; however, its accuracy varies directly with experience in interpretation. There has not been a large enough series yet reported for the acuity of the observer to have been stabilized. For this reason we would hesitate, at this premature date, to recommend its routine use. Many more tests will have to be performed before any consistency in results will be assured.

There is one situation in which the nucleogram has proved of undeniable value even at this early date, namely, where disk pathology is suspected in the absence of localizing neurologic signs, and the patient has failed to respond to the best of conservative care. If a myelogram done at this point does not exhibit a defect, a nucleogram is indicated. Positive findings diagnose and localize the lesion, and a negative test suggests a nondiskogenic or

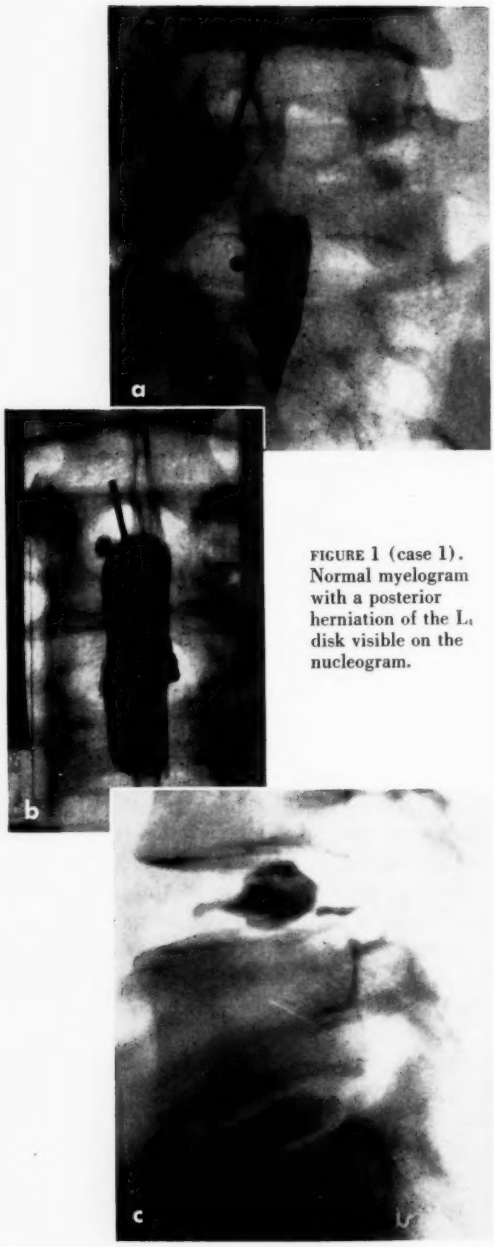


FIGURE 1 (case 1). Normal myelogram with a posterior herniation of the L_4 disk visible on the nucleogram.

functional origin. For the first time we have been able to carry the diagnosis and therapy through to a satisfactory conclusion.

We recently treated a group of patients who had histories suggesting herniated lumbar intervertebral disks but whose clinical findings were equivocal and confused by a certain degree of functional overlay. The myelogram in each case proved negative. Operative intervention was deemed unwise without further evidence, and nucleograms were done. In eight cases, significant protrusions were visualized, and the pain was reproduced at the time of injection of one or both of the lower two lumbar disks. In three others the nucleogram was negative.

Seven of these eight patients subsequently were subjected to surgery with verification of the nucleographic evidence. In three of these there were herniations at both the L_4 and L_5 interspaces, in three only the L_5 level was involved, and one was at L_4. Five have had excellent relief of pain. Another patient, who underwent operation two months ago, has had complete relief of the original symptoms on the right side, but some pain has developed in the opposite hip. Not enough time has elapsed for evaluation of the seventh patient, although he is doing well.

Case Reports

Case 1—A 25 year old clerk injured his back when he slipped at work on November 28, 1954. He was hospitalized for one month because of acute back pain. X-rays of his lumbosacral spine were reported as negative. Following discharge from the hospital he was given heat therapy to his back. Although he improved, he was unable to return to work, and because of recurrence of acute pain he was again hospitalized on January 29, 1955 and placed in traction.

When seen by us on February 5, 1955, the patient complained of severe back pain and pain in the right leg. He moved about in bed with difficulty. A marked scoliosis was noted when he was allowed to stand and there was a tilt of the lumbar spine to the right with spasm of the paravertebral muscles. Tenderness was elicited over the spinous processes

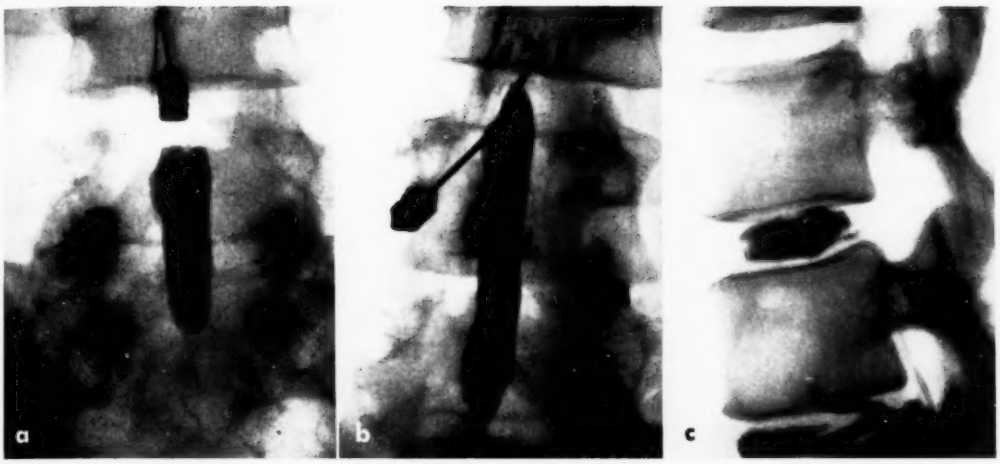


FIGURE 2 (case 2). Large rupture of the fourth lumbar intervertebral disk on the nucleogram in the presence of a normal myelogram.

at L_4 and L_5. Forward and backward bending were definitely limited. The jugular compression test was negative. The straight leg-raising test was markedly positive on the right and slightly positive on the left. No motor, sensory or reflex abnormalities were demonstrated.

It was our impression that this patient had a ruptured intervertebral disk at the L_4-L_5 level. Continued conservative therapy was recommended in the form of hot packs and semi-Fowler's position. Since the patient failed to improve, a myelogram was done on February 19, 1955; it was negative. Spinal fluid protein was 40. Again the patient was continued on conservative therapy. He failed to show any improvement and we were unsuccessful in our attempt to get him out of bed. Accordingly, a nucleogram was done which showed degeneration of the fourth lumbar disk with bulging of the annulus (figure 1). His fourth disk was explored and found to be bulging with thinning of the annulus. There was definite evidence of nerve root compression.

Postoperatively there was dramatic relief of sciatic pain and back pain, although he complained of some leg pain on the sixth day when he was allowed out of bed. Three weeks postoperatively the patient was much improved but complained of occasional mild pain in the right leg. He was allowed to return to work on April 25, 1955.

Case 2—A 33 year old plumber was first seen by us on August 16, 1954 when he complained of pain in the low back and down the right leg. He had injured his back two weeks previously while at work. His pain was aggravated by coughing and sneezing and by movements of his back. About one week later he was admitted to the hospital where he was placed in traction and given heat therapy. While in traction, he noted some improvement in his leg pain but not in his back pain. X-rays of the spine were reported as negative. His past history indicated an episode of back pain following the lifting of a box six years before. Apparently he was incapacitated for four to six weeks at that time.

The patient rested comfortably while in bed, but on getting out of bed he moved with some difficulty. There was tenderness to the right of the spinous processes at L_4 and L_5 and some spasm of the paravertebral muscles. In addition, there was considerable tenderness over the coccyx and moderate limitation of motion on bending forward and backward. There was definite straightening of the normal lumbar curve. The jugular compression test was negative. The straight leg-raising test

was slightly positive on the right and negative on the left. There was questionable hypesthesia in the S_1 root distribution, but there were no motor or reflex abnormalities.

It was our impression that the patient had an acute lumbosacral strain but that a ruptured intervertebral disk should be considered. Conservative therapy was advised in the form of heat therapy and semi-Fowler's position. When this patient showed no evidence of improvement after continued conservative therapy, a myelogram was done on October 7, 1954. This was interpreted as negative. Spinal fluid protein was 40 mg. per cent. Following another period of bed rest, the patient was able to return to work on November 1, 1954.

Because of recurrence of pain, he was again unable to work and when seen by us on March 22, 1955, he complained of acute pain in the back and in the right leg. There was tenderness over the lower lumbar spine as well as over the coccyx. No definite muscle spasm was noted, but there was marked limitation of motion on forward and backward bending. The straight leg-raising test was slightly positive bilaterally. No motor or reflex abnormalities were noted. Sensory loss in the right lower leg in a stockinglike distribution was present.

We felt that this patient had a considerable degree of emotional overlay, but that a ruptured intervertebral disk was a possibility. For this reason, nucleography was advised. This study revealed definite degeneration of both the fourth and the fifth lumbar disks. There was protrusion of the annulus at L_4 with evidence of an extradural extravasation of dye indicating the presence of a tear in the annulus (figure 2).

In view of the nucleographic findings, surgical exploration was done on April 11, 1955 and a protruding disk at L_4 on the right side was found with an opening in the annulus and loose cartilage extruding. At L_5 there was bulging of the disk also, with an intact annulus. Both disks were removed. His response in the immediate postoperative period has been satisfactory.

Summary

1. The history, limitations and inaccuracy of myelography are discussed.

2. The advantages and technic of nucleography in eight cases of ruptured disks with negative myelograms are presented.

3. The nucleographic findings were verified in all seven cases in which the patients were subjected to surgery.

4. The results suggest that the nucleogram is of value in confirming the diagnosis of herniated disk when the clinical picture and myelographic findings are inconclusive.

REFERENCES

1. Dandy, W. E.: Roentgenography of the brain after the injection of air into the spinal canal. Ann. Surg. 70:397-403, 1919.
2. Widerøe, S.: Uber die diagnostiche Bedeutung der intraspinalen Luftinjektionen bei Rückenmarksliedien, besonders bei Geschwülsten. Zentralbl. f. Chir. 48:394-397, 1921.
3. Dandy, W. E.: Diagnosis and localization of spinal cord tumors. Ann. Surg. 81:223-254, 1925.
4. Camp, J. D.: Contrast myelography past and present. Radiology 54:477-505 (April) 1950.
5. Sicard, J. A. and Forestier, J.: Methode generale d'exploration radiologique par l'huile iodee. Bull. et mem. Soc. med. d. hôp. de Paris 46:463-469, 1922.
6. Odin, M., Runström, G. and Lindblom, A.: Iodized oils as an aid to the diagnosis of lesions of the spinal cord and a contribution to the knowledge of adhesive circumscribed meningitis. Acta radiol., 1929 (suppl. 7), pp. 1-80.
7. Radovici, A. and Meller, O.: Encephalographic liquidienne par le thorotrast sous arachnoidien. Rev. neurol. 1:479-485, 1932.
8. Minter, W. J. and Barr, J. S.: Rupture of the intervertebral disc with involvement of the spinal canal. New England J. Med. 211:210-215, 1934.
9. Hampton, A. O. and Robinson, J. M.: Roentgenographic demonstration of rupture of the intervertebral disc into the spinal canal after the injection of Lipiodol; with special reference to unilateral lumbar lesions accompanied by low back pain with "sciatic" radiation. Am. J. Roentgenol. 36:782-803, 1936.
10. Woodhall, B.: Aspiration of Lipiodol injected for diagnosis and localization of ruptured intervertebral discs. North Carolina M. J. 2:655-657, 1941.
11. Kubik, C. S. and Hampton, A. O.: Removal of iodized oil by lumbar puncture. New England J. Med. 224:455-457, 1941.
12. Ramsey, G. H., French, J. D. and Strain, W. H.: Iodinated organic compounds as contrast media for radiographic diagnoses; Pantopaque myelography. Radiology 43:236-240, 1944.
13. Arnell, S. and Lindström, F.: Myelography with Skiodan (abrodil). Acta radiol. 12:287-288, 1931.
14. Arnell, S.: Weitere Erfahrungen über Myelographie mit Abrodil. Acta radiol. 25:408-413, 1944.
15. ———: Myelography with water-soluble contrast, with special regard to the normal roentgen picture. Acta radiol., 1948 (suppl. 75), pp. 1-85.
16. Rees, S. E. and Donley, C. E.: The accuracy of Pantopaque studies in diagnosis of herniated intervertebral disc. Northwest. Med. 48:180-182, 1949.
17. Scoville, W. B., Moretz, W. H. and Hawkins, W. D.: Discrepancies in myelography. Statistical survey of 200 operative cases undergoing Pantopaque myelography. Surg., Gynec. & Obst. 86:559-564, 1948.
18. Raaf, J. and Berglund, G.: Results of operations for lumbar protruded intervertebral discs. J. Neurosurg. 6:160-168 (March) 1949.
19. Lindblom, K.: Diagnostic puncture of intervertebral disc in sciatica. Acta orthop. Scandinav. 17:231, 1948.
20. ———: Technique and results in myelography and disk puncture. Acta radiol. 34:321, 1950.
21. Erlacher, P. R.: Nucleography. J. Bone & Joint Surg. 34B:204-210 (May) 1952.
22. Gardner, W. J., Wise, R. E., Hughes, C. R., O'Connell, F. B., Jr. and Weiford, E. C.: X-ray visualization of the intervertebral disk. Arch. Surg. 64:355-364 (March) 1952.

Common Injuries of the Knee

CHARLES KECK, JR.* AND JOHN P. ADAMS**

George Washington University School of Medicine, Washington, D. C.

THE region of the knee is bounded above by an imaginary line drawn around the thigh at a level 2 in. above the base of the patella. Its inferior extent is at the tibial tuberosity.

The knee is the most massive and vulnerable of the larger joints of the human skeletal system. Two of the longest and strongest bones in the body, the femur and the tibia, meet to form this mechanical unit, thus predisposing it to severe stresses and strains. Furthermore, its superficial position makes it especially prone to external injury. It is therefore not surprising that injuries of the knee occur frequently.

Many of the unstable, incompetent knees which one sees could have been prevented if the physician who was first consulted after injury had made a correct, specific diagnosis and instituted appropriate treatment.

The diagnosis of knee lesions depends on the combination of a careful history and a complete physical and x-ray examination. One must have an accurate knowledge of anatomy and biomechanics and be proficient in interpreting routine and special x-ray projections.

CHARLES KECK, JR.

JOHN P. ADAMS

Since injuries to soft tissues predominate, this article will stress (1) anatomic and physiologic considerations, (2) the significance of symptoms and signs in diagnosis, (3) the clinical examination of the joint and (4) general principles underlying the treatment of these disorders.

Importance of the Quadriceps

The quadriceps muscle is the "watchdog of the knee" (figure 1). It is the most important muscle of the lower limb concerned in maintaining man's erect posture.

*Assistant Resident in Surgery; **Department of Surgery, George Washington University School of Medicine, Washington, D. C.

From an anatomic viewpoint the quadriceps is a composite muscle of four origins with a common insertion. The vastus lateralis, vastus intermedius and vastus medialis arise from the lateral, anterior and medial aspects of the femur. Only the rectus femoris arises from the pelvis where it is attached by two heads in front of and above the acetabulum.

Except for the hip flexion produced by the rectus femoris, the action of the quadriceps is solely that of extending the knee. Functionally, extension is performed primarily by the vastus muscles, of which the medialis is the most powerful. Furthermore, the vastus medialis is almost selective in action in producing the last 10 to 15 degrees of extension. In spite of this small operational range, the vastus medialis is by far the most important component of the quadriceps apparatus. It is primarily this muscle which stabilizes the joint and protects it from injury.

The bracing of the knee joint in full extension by the quadriceps is biologically of recent origin. Complete extension of the knee is common only to man and the elephant. Nature did not endow man with new muscles for this function. She merely imposed orthograde functions on muscles which previously had performed plantigrade motion. A study of evolutionary processes discloses that man loses first those functions last evolved. The responsibility of the vastus medialis for maintaining the final 15 degrees of extension is one reason why characteristic atrophy of the medialis component is seen first in organic disorders of the knee (figure 2). Thus the vastus medialis is truly the "key to the knee."

Since the quadriceps stabilizes the knee joint in varying positions of flexion, produces powerful extension and helps maintain equilibrium, it is not surprising that protection of the joint from injury should depend in large measure on muscle tone. Furthermore, few muscles lose tone so quickly as does the quadriceps following injury to the knee joint. Thus one can readily appreciate the necessity for prompt attention to quadriceps drill following injuries to the knee. A quadriceps strengthened by progressive exercises can often stabilize the knee quite adequately following a collateral or cruciate ligament tear. For this reason every patient should be given precise instructions in quadriceps drill preferably before and always after operation or injury. It is often wise to start quadriceps exercises several days before operation, resuming them immediately after surgery.

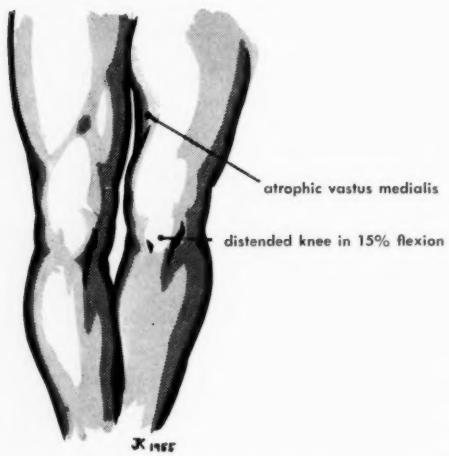


FIGURE 1. The injured knee. Note the distended knee held in 15° of flexion. Quadriceps wasting is most pronounced in the vastus medialis component.

Traumatic Synovitis and Hemarthrosis

The synovial cavity of the knee joint is the largest in the body and consists of a fibrous tissue sac lined with synovial cells (figure 3). Its inferior cavity encloses the articular surfaces of the femur, tibia and patella. The superior cavity, or suprapatellar pouch, extends upward between the quadriceps tendon and the femur. When distended with effusion it can hold about 80 cc. of fluid. Its capacity rises to 100 cc. or more when the knee is held in a position of 15 degrees of flexion.

Acute traumatic synovitis is a sequela of most acute knee injuries. Following trauma a characteristic response is initiated in the synovial membrane which disrupts the normal interchanges between the blood and lymphatic systems. The rich vascular bed in the subsynovial stratum undergoes dilatation or disruption, leading to extravasation of plasma and

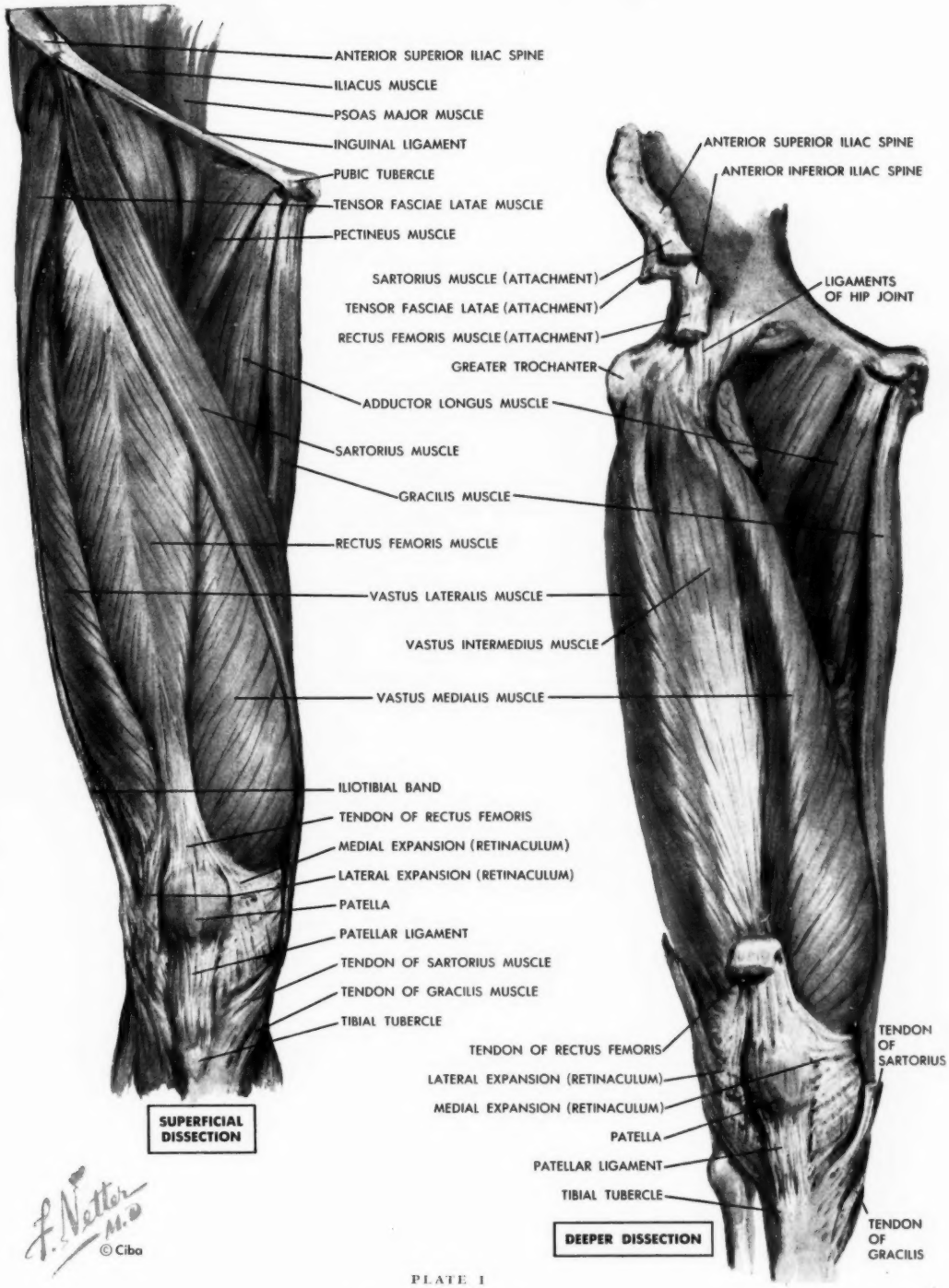


PLATE I

FIGURE 2. Musculature of the knee.

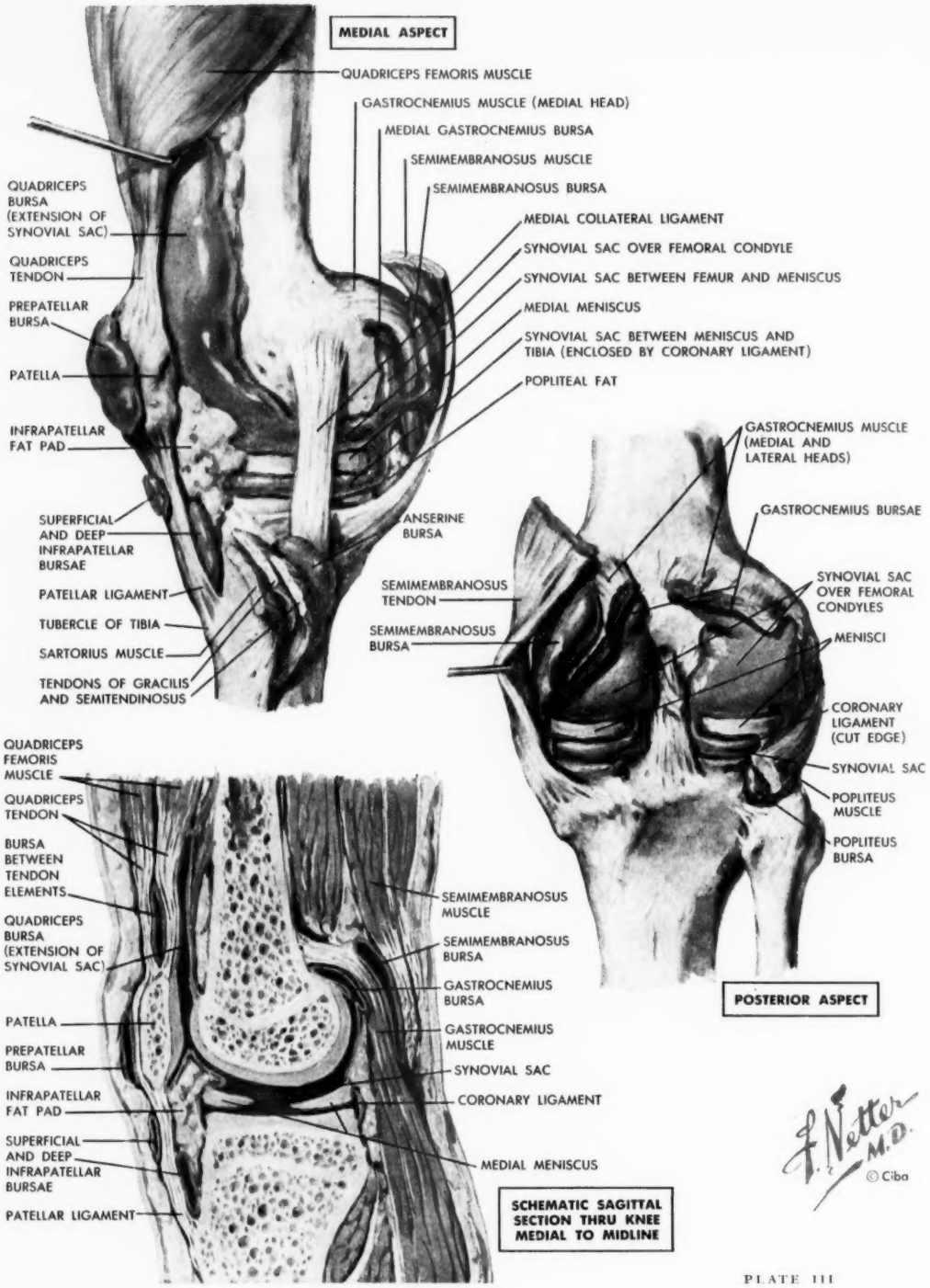


PLATE III

FIGURE 3.

(Figures 2 and 3 are reprinted from CIBA *Clinical Symposia.*)

blood constituents into the joint. The lymphatics, on the other hand, undergo obliteration due to the increased intra-articular pressure. Thus the lymphatic system is rendered incapable of removing the harmful metabolic and debris products. As the acid metabolites increase, the joint acidity increases. This leads to the precipitation of blood colloids, especially fibrin, which lays the foundation for the formation of granulation tissue. Adhesions may develop subsequently, especially if the normal range of knee motion is restricted due to muscle spasm caused by pain. Thus a "frozen knee" may result. In addition, the specialized synovial cells are stimulated to increased activity by the mounting chemical irritants, resulting in an increase in the mucin content of the fluid and hypertrophy and increase in the number of cells. The entire synovial membrane thus becomes thickened, hyperplastic, hyperemic and edematous.

The clinical features of traumatic synovitis are varying degrees of distention of the joint capsule, discomfort and limitation of movement. In acute traumatic synovitis, an interval of at least six hours usually elapses between the injury and the appearance of the swelling. This feature differentiates the lesion from hemarthrosis in which swelling of the joint is demonstrable within one-half to one hour after injury. The swelling outlines the horseshoe shape of the suprapatellar pouch and floats the patella off the femoral condyles. Tapping the center of the patella with the finger elicits a click as it strikes the anterior surface of the femoral condyles and thus the "patella tap" is produced.

Since the synovial membrane is not a major source of articular sensation, effusion usually produces a sensation of distention and discomfort rather than true pain. Severe pain usually indicates injury to the periosteum or ligament.

Treatment consists of rest, aspiration, compression, ice bags and quadriceps drill. Small effusions with minimal distention of the capsule may be treated with a snug elastic compression bandage and partial restriction of weight bearing. Massive effusions should be aspirated since they interfere with the circulation, both venous and lymphatic (figure 4). After the joint is decompressed, it is often helpful to inject 5 cc. of 2 per cent XYLOCAINE® mixed with 2 ampules of hyaluronidase. This helps to relieve pain and aids in the absorption of undesirable reactionary products. A compression bandage is then applied and ice bags prescribed. In all cases progressive exercises of the quadriceps muscle are instituted immediately to prevent rapid and disabling atrophy of the quadriceps muscle. Only in acute hemarthrosis is motion restricted for several days to minimize the risk of further hemorrhage.

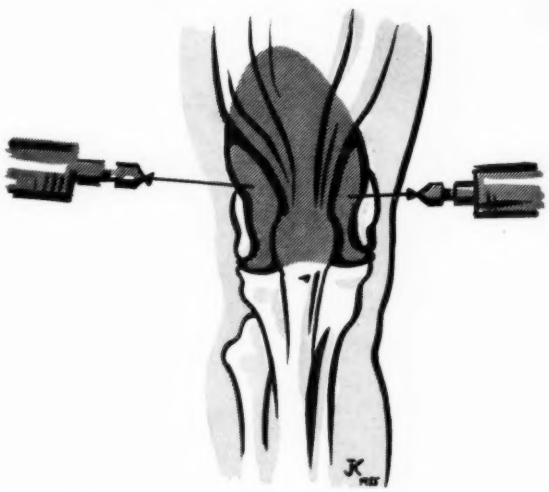


FIGURE 4. Technic for aspirating the knee joint.

Prepatellar Bursitis

The prepatellar bursa is interposed between the skin and patella (figure 3). It may rest within the subcutaneous areolar tissue or under the fascia lata, or actually within the substance of those fibers of the quadriceps tendon that pass across the front of the patella. It is therefore referred to as the subcutaneous, subfascial or subtendinous prepatellar bursa, according to the depth at which it lies buried in connective tissue.

Direct trauma to the prepatellar bursa is

very common and is often followed by distention of the cavity by effusion or blood. Puncture wounds into this area may introduce virulent organisms, leading to a suppurative bursitis. Repeated trauma, such as that sustained in certain occupations, may cause thickening of the bursal walls and accumulation of fluid.

Other conditions, such as gouty, tuberculous, syphilitic, arthritic and neoplastic bursitis, should be considered before therapy is instituted for a presumed traumatic bursitis.

Treatment of traumatic bursitis usually consists of removing the cause. If the initial inflammatory response does not subside without therapy, aspiration, compression bandages and restricted activity may be used to speed recovery. Suppurative bursitis should be treated with rest, continuous hot fomentations and the administration of systemic antibiotic

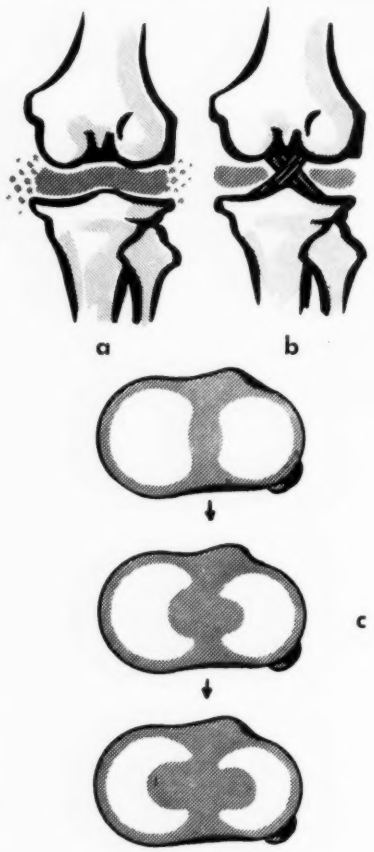
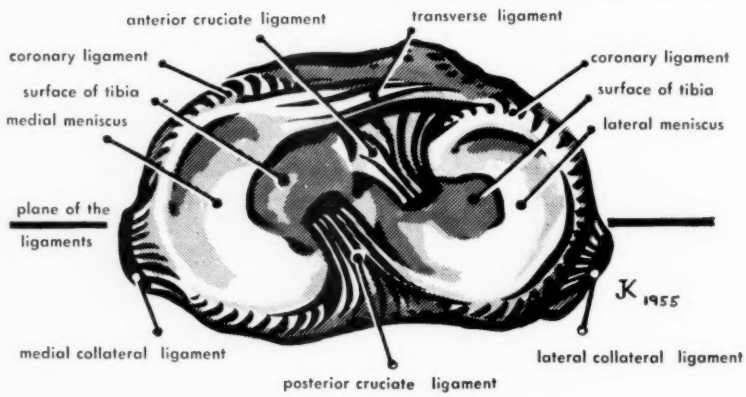


FIGURE 5. Embryologic development and anatomy of the medial and lateral menisci.

a. Condensation of undifferentiated mesenchyma to form primitive mesenchymal plate.

b. Transverse division of the mesenchymal plate by the development of the cruciate ligaments.

c. Molding of the infantile menisci into adult form.



SUPERIOR ASPECT OF TIBIA

agents. The local injection of 25 to 50 mg. of hydrocortisone has been found to be effective in chronic traumatic bursitis.

Injuries of the Semilunar Cartilages

Embryologic development—By a process of selective differentiation the intra-articular menisci develop from the undifferentiated mass of mesenchymal cells that first constitutes the knee. This flat mesenchymal plate (figure 5a), which first divides the joint into a superior and an inferior cavity, is later split centrally by the development of the embryonic cruciate ligaments (figure 5b). The solid discoid menisci thus produced undergo liquefaction of their central portions in the latter half of fetal life. At about the fourth year the menisci assume their adult shape (figure 5c). Arrests in this developmental process, from cushions to partial rings, account for the various forms of congenital discoid cartilages.

Anatomy—The menisci rest on the tibial plateau and are bound to its margins by the coronary ligament (figure 5). The meniscus lateralis forms a large segment of a small circle, whereas the meniscus medialis forms a small segment of a large circle. The meniscus lateralis is smaller, thinner and less firmly attached to its adjacent collateral ligament than the meniscus medialis. Both are attached anteriorly and posteriorly to the nonarticular part of the upper surface of the tibia.

The blood supply reaches the peripheral portions of the menisci through the fibrous tissue of the true capsule which blends intimately with the menisci at their periphery. The central portions of the menisci are avascular and depend for their nutrition on the synovial fluid.

Motion of the menisci—In spite of their numerous attachments the meniscal cushions are quite mobile. However, the excursion of the internal meniscus is less than that of the external, because it is firmly anchored to the tibial collateral ligament at a point just posterior to its center. This restricted motion of the internal meniscus is primarily responsible for making it more vulnerable to injury than its lateral counterpart during forceful rotary movements of the knee joint in flexion.

The menisci migrate forward on extension and backward on flexion of the knee (figure 6a). This motion takes place between the inferior surface of the meniscus and the corresponding articular surface of the tibial plateau. Furthermore, during the final 5 degrees of extension the menisci rotate counterclockwise. In early flexion the rotation is clockwise.

The points of contact between the femoral condyles and the menisci are also constantly changing. During extension the femoral condyles rest on the anterior segment of the menisci. In flexion the weight is borne on the posterior segments.

Injury to the menisci—The factors responsible for isolated injury to the menisci are flexion, rotation and weight bearing.

When the femur is rotated internally with the knee flexed and the tibia fixed, the posterior segment of the internal meniscus snaps into the interior of the posterior compartment of the joint. If at this point the knee is extended, the posterior segment is crushed between the femoral condyle and the tibial plateau, producing a posterior segmental tear, usually of the longitudinal type (figure 6b). When the femur is rotated externally with the knee flexed and the tibia fixed, the meniscus medialis is swept forward and centrifugally. If the knee is then extended, severe traction is made on the posterior capsular attachment and is apt to cause a peripheral tear of the posterior segment or its capsular attachment (figure 6c). Injuries to the meniscus lateralis may also occur during these periods of abnormal stress but are less frequent because of the freedom of movement of this fibrocartilage enabling it to slide free of harm.

Stretching or rupture of the peripheral meniscal attachment is the precursor of the meniscus lesion since central displacement of the fibrocartilage cannot occur without it. As an isolated lesion this injury produces synovial effusion or hemarthrosis associated with point tenderness at the site of trauma. Flexion and extension of the knee may be limited by muscle spasm induced by pain. When the central displacement is accompanied by a tear of the meniscus, locking may occur. If the tear involves the posterior third of the meniscus

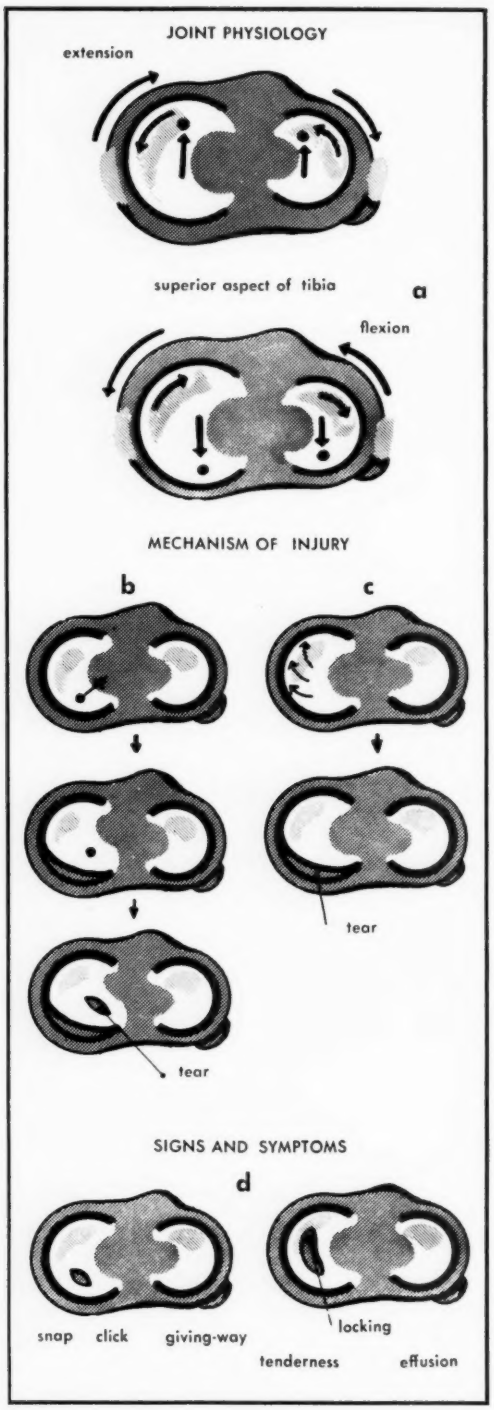


FIGURE 6. Movements of the meniscal cushions and mechanism of injury.

a. During extension of the knee the menisci move forward and rotate medially. The tibia rotates laterally. The femoral condyles rest on the anterior segments of the menisci (indicated by black dot). During flexion the movements are reversed.

b. Displacement of posterior segment of medial meniscus into center of joint during abnormal rotary movement with the knee in flexion. With extension of the knee the posterior segment is crushed between the femoral condyle and the tibial surface leading to a posterior segmental tear.

c. Displacement of the medial meniscus anteromedially with resultant posterior marginal tear.

d. Locking occurs when the femoral condyle strikes the centrally displaced meniscal fragment during extension.

only, the entire meniscus usually springs back into normal position following injury and the joint does not lock. If the tear extends anteriorly beyond the plane of the collateral ligaments, the femoral condyle traps the centrally displaced wedge fragment against the tibia. Further extension is then impossible and the joint is said to be locked.

Other diagnostic features may also be elicited (figure 6d). The sensation of a click or snap occurring within the joint associated with a sickening pain usually indicates the tearing of a meniscus or the complete rupture of a ligament. "Giving-way," which usually indicates a longitudinal tear of the posterior segment of a meniscus, may be the description given in a case in which the knee suddenly collapses when the patient turns suddenly or walks on uneven ground. Furthermore, effusion is always present following the original accident. If effusion does not occur, the diagnosis of a torn cartilage is incorrect.

Healing of the torn meniscus is slow and the prognosis with conservative treatment is poor because of inadequate blood supply. The observations made by King (1936) regarding the healing of experimentally produced tears of the menisci in dogs are as follows:

1. Tears which are limited to the semilunar cartilages probably never heal.

2. A torn meniscus can be healed by connective tissue if the tear communicates with the synovial membrane laterally or medially.

3. A complete transverse or oblique tear results in some separation of the fragments, but the intervening space fills in with connective tissues arising from the synovial membrane. This connective tissue is quite firm in three weeks, which suggests the length of time necessary for complete fixation in these cases.

4. If the meniscus is partially torn from its peripheral attachment, it heals in normal anatomic position without difficulty.

Treatment—It has been aptly said that "there are more displaced diagnoses than cartilages." A conservative regimen should therefore be the rule during the initial period of therapy.

Treatment of the locked knee is immediate reduction. Usually this may be accomplished within the first 24 hours following the initial injury by simple traction on the leg with the knee in flexion. This allows the displaced fibrocartilaginous fragment to spring back into place. If, however, the joint has been locked for more than 24 hours the normal tissue elasticity is lost and the displaced fragment may not assume its normal position without considerable manipulation.

For the acutely painful knee, bed rest with Buck's traction is usually best. As the joint effusion subsides, a plaster cylinder may be applied to the leg with the knee in extension. The patient is usually able to walk during this stage of recovery. Therapy should be extended over a three week period as indicated by King's work. If this therapeutic regimen fails, surgery is next to be considered.

Injuries to Ligaments

Second only in importance to active muscular control in maintaining perfection of function in the knee joint is the passive control of the ligaments. These not only determine the direction in which muscle action is transmitted to the moving surfaces, but also achieve, through their sensory nerve fibers, the coordination essential to the protection of the joint from injury. The functions of the anterior and posterior cruciates are closely interrelated with those of the medial and lateral ligaments. It is therefore difficult to ascribe a specific function to any particular ligament since they work as a closely interrelated unit in maintaining the integrity and stability of the joint. This close interrelationship also helps to explain the infrequency of serious isolated ligamentous injuries of the knee. A complete rupture of the tibial collateral ligament is commonly associated with rupture of the anterior cruciate ligament and tearing of the internal meniscus. If the true nature of these severe injuries is understood, adequate treatment will follow. The assumption that immobilization of the knee in a plaster cylinder for four weeks will allow adequate healing of a serious ligamentous injury is incorrect and may lead to irreparable harm. Immediate surgical repair is far superior to conservative treatment in these cases.

Cruciate ligaments—The cruciate ligaments are tough round fibrous bands located in the center of the knee joint connecting the femur and tibia (figure 7). They cross each other like the limbs of a St. Andrew's cross and stabilize the tibia and femur in their anteroposterior glide on one another. Their names are derived from their tibial attachments. The anterior cruciate ligament prevents backward displacement of the femur and hyperextension of the joint. Hyperextension of the knee may rupture the anterior cruciate. The posterior cruciate ligament prevents forward displacement of the femur on the tibia and is tight on flexion. Rupture of this ligament permits the tibia to assume a position of posterior displacement on the femur when in flexion. Clinically both ligaments are tested by the "drawer sign."

Collateral ligaments—The collateral ligaments are attached above to the femoral epicondyles. Below they are attached far back—the tibial collateral ligament to the surface of the tibia adjacent to its medial border, the fibular collateral ligament to the head of the fibula just in front of its apex (figure 8). When the knee is extended the ligaments are taut. During flexion the collateral ligaments are slack and, therefore, permit medial and lateral rotation.

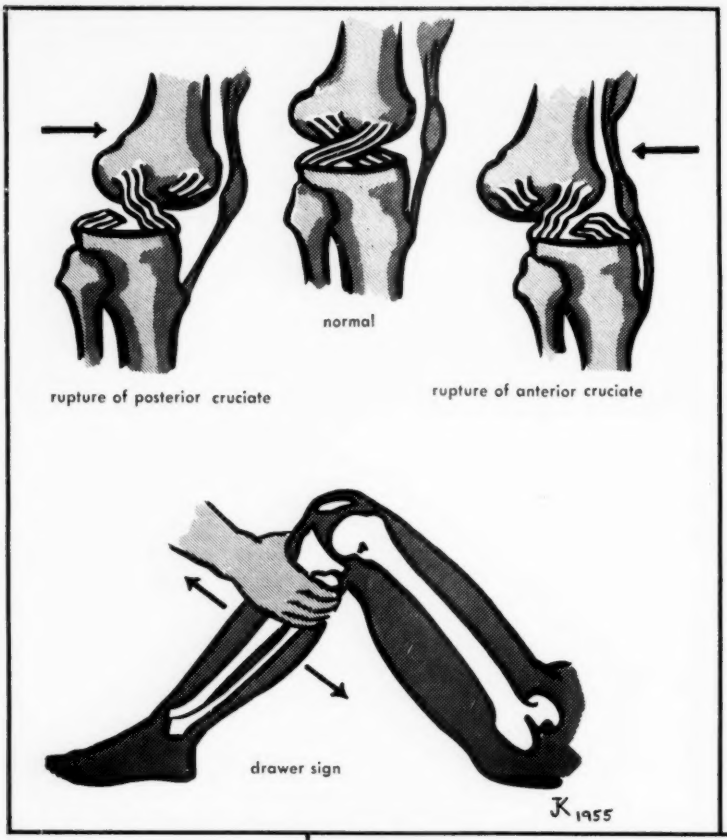


FIGURE 7. The anterior and posterior cruciate ligaments. The *drawer sign* is used to test for stability of the anterior and posterior cruciate ligaments.

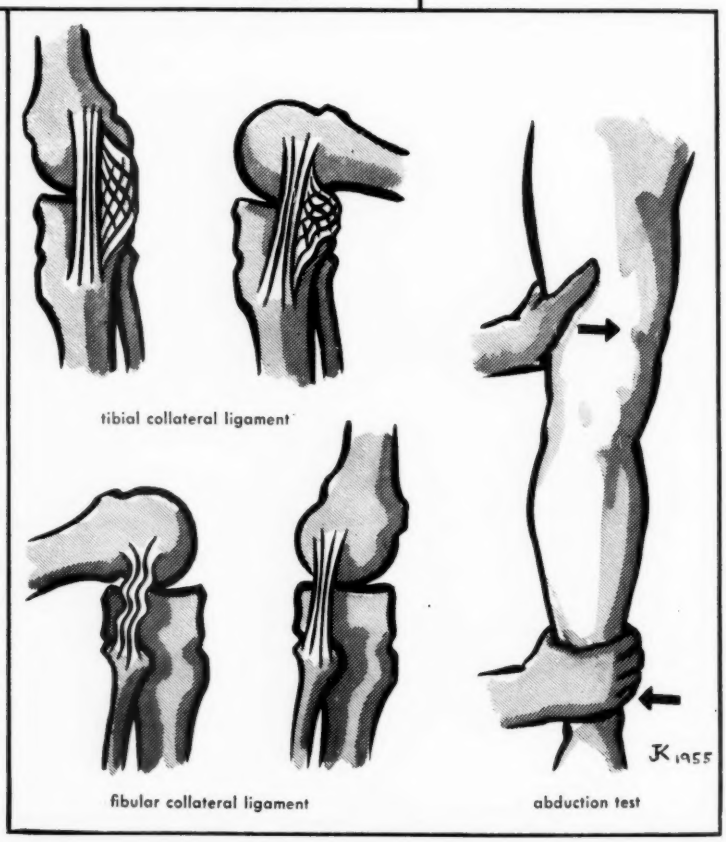


FIGURE 8. Tibial and fibular collateral ligaments. Note that the ligaments are taut on extension and relaxed on flexion. Therefore, when testing for medial and lateral stability the knee should be in the extended position.

The tibial collateral ligament takes pride of place because its frequency of injury is greater than that of any of the other ligaments of the knee joint. Furthermore, the disability resulting from complete rupture of this ligament is the most potentially disabling since it is usually associated with rupture of the anterior cruciate ligament, loss of the peripheral attachment of the meniscus medialis, and fracture of the lateral condyle of the tibia.

Twisting injuries, such as occur in skiing accidents and football games, account for the majority of tibial collateral ligament sprains or ruptures.

A sprain or partial avulsion of the medial collateral ligament usually occurs at its attachment to the femur. On examination, swelling over the medial aspect of the femoral condyle with vague tenderness in the line of the collateral ligament is found. The point of maximum tenderness is definitely localized to the femoral attachment. This injury is distinguished from complete rupture by placing the ligament on the stretch in attempting to abduct the joint in extension (figure 8). Pain will be produced at the upper femoral attachment, but joint stability is unimpaired.

Complete ruptures usually follow blows against the unprotected lateral aspect of the joint. The resulting pain and disability are severe. The joint becomes distended with effusion or blood. Positive diagnosis is based on the presence of abduction of the joint in extension. Other associated injuries may be present and should not be overlooked.

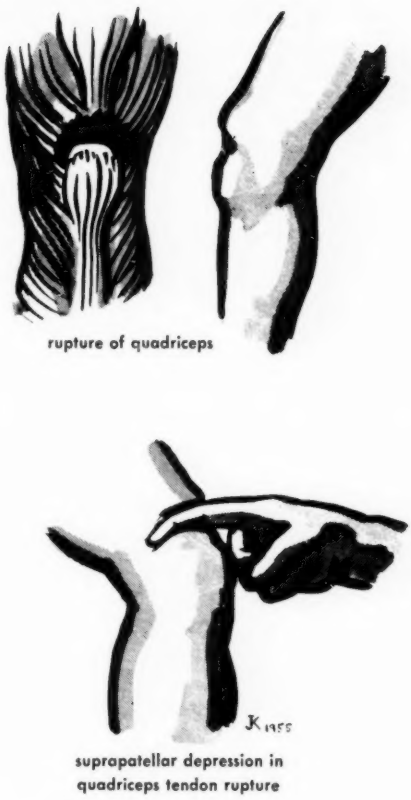


FIGURE 9. Rupture of quadriceps.

Disruptions of the Extensor Apparatus

Disruptions of the extensor apparatus of the leg are common and include fractures of the patella, rupture of the quadriceps tendon, rupture of the patellar ligament and avulsion of the tibial tuberosity. Fracture of the patella is about 80 times as common as ruptured quadriceps, but the latter is in turn much more frequent than rupture of the ligamentum patellae. Avulsion of the tibial tuberosity commonly occurs in the younger age groups.

Quadriceps tendon rupture—Rupture of the quadriceps muscle or tendon ranks second in frequency of all tendon ruptures (figure 9). Nevertheless, like all subcutaneous ruptures of tendons, the diagnosis is frequently missed and thus the injury is inadequately treated. Although this injury may occur in persons of all age groups, it is more commonly associated with the older age groups. Presumably the degenerative changes of advancing years weaken the tendon, which generally breaks near its insertion. A direct blow is the usual cause, as when a person falls on the flexed knee. The resultant sudden, violent quadriceps contraction tears the tendon.

The diagnosis is suggested by inability of the patient to extend his knee actively. The pathognomonic sign of suprapatellar rupture of the quadriceps tendon is the absence of normal fullness of the quadriceps pouch. A

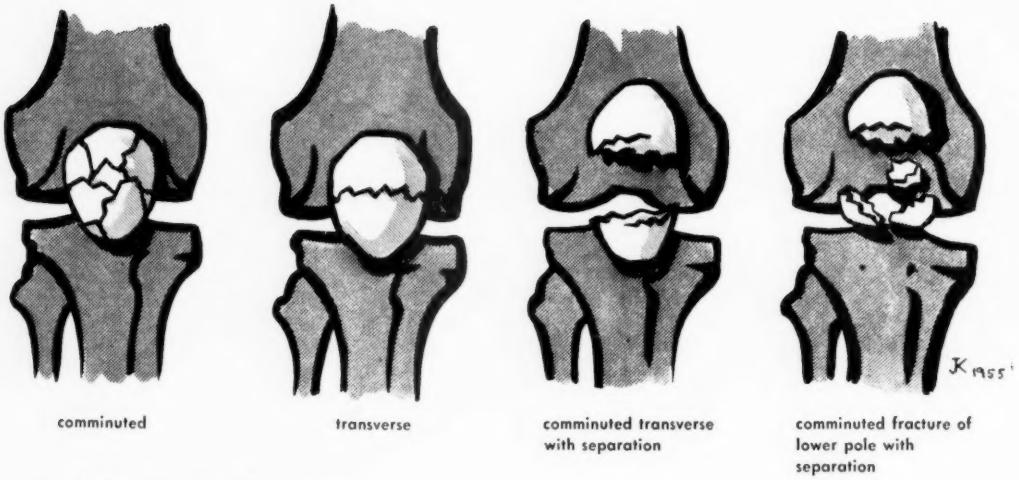


FIGURE 10. Fractures of patella.

hemarthrosis resulting from the injury may, however, fill in this gap and mask this important sign. The demonstration of a gap in the tendon on physical examination will usually disperse all doubts. A lateral x-ray of the knee may be of value in demonstrating the gap, and, in addition, the superior border of the patella is usually seen to tilt anteriorly.

Early operative treatment offers the best chance of regaining normal power following complete rupture of the quadriceps tendon.

Fracture of the Patella

Fractures of the patella are relatively frequent lesions. Those caused by direct violence are stellate or comminuted (figure 10). Since the articular surface is often fractured or contused as a result of the sudden blow against the femoral condyles, sequestration of the articular cartilage may occur. The resultant fragments that form may grow, leading to troublesome "joint mice." Fractures caused by indirect violence are usually of the transverse type. The bone is broken by buckling over the femoral condyles with the knee in flexion. Separation of the fragments occurs when the force is great enough to lacerate the lateral expansions of the quadriceps.

One should have no difficulty in establishing the diagnosis of fracture of the patella. The diagnosis is made by the history, the subsequent disability, the physical examination and finally confirmation by x-ray.

Treatment—Severely comminuted fractures with displacement are best treated by complete patellectomy. In transverse fractures involving one-third to one-half of the patella the distal fragments should be excised and the patellar ligament sutured to the proximal fragment. The quadriceps expansion must be carefully explored, and, if torn, accurately approximated. Undisplaced patellar fractures should be immobilized in a walking cylinder.

Summary

The general principles underlying the diagnosis and treatment of the more common knee injuries have been stressed. Early, correct, specific diagnosis and the institution of immediate appropriate treatment are imperative.

One should again be reminded of the importance of the extensor musculature in maintaining the stability and movement of the knee joint. Therapeutic results following traumatic disorders will be greatly improved by enforcing quadriceps exercises.

Congestive Heart-failure: Prevention and Treatment

CLAYTON B. ETHRIDGE*

George Washington University School of Medicine, Washington, D. C.

CLAYTON B. ETHRIDGE

How important a problem is congestive heart-failure, and how effectively are we employing all currently available measures for its prevention and treatment? It has been recently stated that we have in this field more knowledge than we use.[1] It is, of course, highly necessary that we continue to decry and seek diligently to correct, through research and clinical investigations, serious gaps in our existing knowledge concerning the diseases of the heart, their causes and their prevention. But while we await future developments along these lines, let us carefully seek to utilize in every practical way the not inconsiderable knowledge we already have regarding the management of congestive heart-failure. For this purpose it would seem desirable also that we each take time occasionally to view this problem in broad perspective—that we may realize more clearly our responsibilities and objectives.

In this review it is my purpose to consider the problem of congestive heart-failure in its general aspects. No attempt will be made herein to discuss details of mechanisms, or of drugs, dosages or procedures related to the subject. For information of this latter sort, the appended references may be used to excellent advantage, if so desired.

Statement of the Problem

Congestive heart-failure, whether of gradual or sudden onset or of mild or severe degree, is the most common clinical manifestation resulting from the different kinds of diseases of the heart, regardless of their respective primary causes or their particular types of cardiac injury. Moreover, the diseases of the heart, collectively, constitute the major cause for mortality and for serious morbidity and disability in this country at the present time. It results, therefore, that, for the average physician in internal medicine or general practice, the recognition and management of congestive heart-failure represent a very frequent and most important task, concerning which it behooves him to be well prepared. Each of us should be acutely alert to the magnitude of

*Department of Medicine, George Washington University School of Medicine, Washington, D. C.

this problem and to its numerous ramifications, for only thus can we each contribute our fair share to its mitigation in these times.

Fortunately, research and clinical experience over the past 25 years have produced a considerable increase in our knowledge regarding diseases of the heart. Newer technics and clearer comprehensions now permit their more accurate recognition and differential diagnosis,[2] and a better, if still incomplete, understanding of their pathophysiologic effects.[3] Moreover, we now possess a group of well-tried drugs and procedures[4-7] that, when timely and wisely applied, are usually effective in modifying favorably, for long periods of time, the course of most patients with congestive heart-failure. To secure such good results as frequently as possible, we need to comprehend clearly certain basic concepts; we need to exert anticipation and diligence in applying the various therapeutic measures currently at our command; and we need, of course, proper patient understanding and cooperation. All too often our failures occur because not enough attention has been devoted to this latter consideration—and this applies equally to individual private patients as well as to groups of patients in large cardiac clinics. Fitted into this general framework, however, the management of diseases of the heart, and of congestive heart-failure, can be, in the larger sense, one of the most satisfying experiences of modern medical practice.

Prevention of Heart Diseases

Ideally, the problem of congestive heart-failure would be best controlled by preventing the primary causes of heart disease. Since some 40 different etiologic bases for heart disease are now known,[1] their recognition and comprehension, as well as their possible prevention in certain instances, involve the whole scope of medicine. More specifically, however, we still lack practical or certain means for the prevention of the five most common kinds of heart disease, those of congenital, rheumatic, syphilitic, hypertensive and arteriosclerotic origins. Yet, certain beginnings of knowledge in that direction have been made, and these deserve our full respect and attention. The probable relationship between maternal German measles during the first trimester of pregnancy and the occurrence of certain congenital cardiac anomalies in the developing fetus is an interesting example of such beginnings. The prevention of initial or recurrent attacks of rheumatic fever through the therapeutic or prophylactic use of antibiotic agents directed against streptococcal throat infections[8] offers considerable promise in this respect and needs wider and more careful application.

Syphilitic infection can now be better and more practically treated than ever before by employing penicillin. With a thorough application of this knowledge, it appears possible that syphilitic heart disease could be virtually eliminated from our population in the not too distant future. Indeed, an obvious lessening of its incidence has already been observed. It seems likely, also, that the proper use, singly or in combination, of the variety of antihypertensive drugs currently available can effect at least some amelioration of the total problem of hypertensive heart disease. In any event, from present indications, considerable hope lies in that direction. On the other hand, our current knowledge of arteriosclerosis, its causes and its prevention leaves much to be desired, despite the intensive and extensive investigations of this condition now going on. Here, for the present, we must be content to work by indirection in an effort to alleviate the degree of arteriosclerosis through control of such aggravating conditions as obesity, diabetes and hypertension, because other efforts at the prevention of arteriosclerosis and arteriosclerotic heart disease must be regarded as experimental rather than truly practical at this time.[9]

Heart disease or congestive heart-failure, the result of thyrotoxicosis, can be prevented or controlled by the early recognition and prompt treatment of the thyroid condition, using for this purpose one or another of several available methods as seems indicated. Other endocrine diseases affecting the heart and its functions, as pheochromocytoma and adrenocortical dysfunction, are currently susceptible to more accurate diagnosis and effective therapy. Beriberi and other forms of

nutritional heart disease are preventable—or curable when recognized early. Acute and subacute bacterial endocarditis are commonly preventable or curable by using suitable antibiotics prophylactically in relation to dental, obstetric and surgical procedures, or therapeutically for early control of existing infections. Acute and chronic cor pulmonale are preventable in many instances by early recognition plus diligent and effective control of their underlying causes.

Modern cardiovascular surgery[10] has much to offer for the prevention or control of certain forms of heart disease. The early recognition and surgical correction of arteriovenous fistulas, of patent ductus arteriosus, of coarctation of the aorta, and indeed of isolated pulmonary stenosis, of interatrial septal defects, of aortic rings, and of constrictive pericarditis, may be regarded as, in certain instances, preventive or curative of heart disease when timely applied. Similarly, current surgical efforts directed against certain forms of chronic valvular heart disease are, broadly speaking, preventive procedures, since in proper circumstances they may bring about striking benefit in alleviating progression of and in controlling heart-failure. This applies at present particularly to selected instances of mitral stenosis, but with some promise of benefit for other valvular lesions as well.

In this field of prevention, then, it should be evident that our responsibilities are great. We have much knowledge, some of which has not been fully evaluated or utilized. But our thinking must encompass an acute alertness to the fact that many diseases and conditions can cause or aggravate heart disease, or cause or precipitate congestive heart-failure. We must recognize that modern therapeutic approaches are numerous and varied, and often strikingly effective. Here it should be emphasized that there exist today, within the near vicinity of every community, medical centers where the accurate diagnosis and often the effective treatment of obscure forms of heart disease (particularly, but not exclusively, those of congenital origin) can be readily accomplished. We have a responsibility to see that such special facilities are early utilized, whenever for any reason the exact nature of a cardiac lesion or its proper treatment is unknown or uncertain.

Precipitating Causes of Heart-failure

Factors capable of precipitating or causing heart-failure may be intrinsic or extrinsic to the heart itself. It is, of course, obvious that intrinsic cardiac changes, such as myocarditis, valvulitis, a ruptured valve leaflet, coronary insufficiency, or a fresh myocardial infarction, can cause heart disease or aggravate an existing cardiac condition and thus cause congestive heart-failure. Included in this category of intrinsic causes are also certain cardiac arrhythmias, particularly those that provoke rapid ventricular response, such as auricular or nodal tachycardia, auricular flutter or fibrillation and ventricular tachycardia. On the other hand, in the presence of existing heart disease of whatever etiologic origin, factors extrinsic to the heart itself may, in many instances, be dominant in precipitating heart-failure by producing stress on the heart and circulation sufficient to disrupt pre-existing cardiac compensation. In this category of extrinsic factors may be listed excessive physical effort or exertion; high emotional stress or excitement; systemic infections, particularly those causing a high fever or severe cough; overeating, especially if it provokes gastrointestinal upsets (as with underlying gallbladder disease, etc.); pregnancy; hyperthyroidism; hemorrhage or severe anemia; serious body trauma; surgical operations and anesthesia; pulmonary embolism; emphysema of marked degree; tension pneumothorax; agitation from severe pain; and, not last or least, excessive sodium intake for any reason.

In the evaluation of any cardiac patient, or whenever congestive heart-failure is encountered, the accurate appraisal of such precipitating factors, extrinsic as well as intrinsic, is obviously indicated. In all such circumstances, in addition to the treatment of the congestive heart-failure per se, concomitant correction or management of the precipitating factor or factors is of extreme importance. Moreover, in terms of the anticipation and prevention of congestive heart-failure in known cardiacs,

efforts at controlling these precipitating factors, as practically and as effectively as we can, should receive our constant attention. Indeed, it should not be forgotten that the occurrence of significant heart-failure itself often costs a high price in its effect on the myocardium, the payment of which may be impossible of accomplishment in particular cases, or in other instances involve considerable effort, plus long disability for the patient.

Therapeutic Principles in Congestive Heart-failure

When expressed as general principles, our efforts in the treatment per se of congestive heart-failure are largely directed toward two major objectives, namely, the improvement of cardiac efficiency and the reduction of demands on the heart. In actual practice, of course, a single therapeutic procedure may have beneficial effects jointly on these two mechanisms.

For the improvement of cardiac efficiency, the digitalis glycosides have a value par excellence.[11] Many different digitalis preparations are now available for this purpose, including those for intravenous as well as oral use. The wise employment of these several preparations requires a proper knowledge of their individual pharmacologic properties, including their different therapeutic and toxic dosages, and their different rates of absorption and excretion. The digitalis preparations have also a considerable value for the control of particular arrhythmias.[12] Quinidine and PRONESTYL® likewise have their proper place for this purpose.

For reduction in demands on the heart, a host of drugs and procedures are available, to be employed as needed in particular circumstances. Of special importance for this purpose, in the average circumstance, is the securing of adequate rest and relaxation for the patient, plus the relief of pulmonary as well as peripheral edema through the control of sodium intake with low salt diets, and the use of diuretics (including the mercurials, DIAMOX®, MICTINE®, ammonium chloride, xanthines, etc.) as indicated. Oxygen administration is warranted in the more critical situations.

Prompt management of systemic infections with chemotherapeutic or antibiotic agents is a frequent must. The effective management of thrombo-embolic phenomena, particularly of pulmonary embolization and infarction, with anticoagulants is essential in certain instances. Adequate knowledge of drugs for this purpose and of available means to control their dosage is therefore commonly necessary. The treatment of anemias by transfusions or other means, as indicated, is sometimes important. The recognition and relief of endocrine stresses, particularly hyperthyroidism, must receive their share of attention. Correction of obesity, the use of paracentesis or phlebotomy, and the careful employment of hypotensive agents, each at times may be found necessary for particular circumstances. As previously discussed, the use of cardiovascular surgical procedures in selected cases often has an important place in reducing the demands placed on the heart.

The drugs and procedures currently available for the management of congestive heart-failure are many and varied, but the principles governing their need and their employment are usually relatively simple and self-evident. When our attention is focused sharply on such principles, better and more prompt therapy for congestive heart-failure will usually result.

REFERENCES

1. Stead, E. A., Jr.: Heart failure. In: Proceedings, First National Conference on Cardiovascular Diseases. New York, American Heart Association, 1950, p. 157.
2. Levine, S. A.: Clinical Heart Disease. Philadelphia, W. B. Saunders Company, 1951, ed. 4, p. v.
3. Katz, L. N.: Mechanism of cardiac failure. Circulation 10:663 (November) 1954.
4. Burch, G. E.: Cardiology for the general practitioner. J.A.M.A. 157:1073 (March 26) 1955.
5. Blumgart, H. L.: Management of congestive heart failure. Circulation 7:127 (January) 1953.
6. Vogl, A.: Use of mercurial diuretics in congestive heart failure. Mod. Concepts Cardiovas. Dis. 24:263 (March) 1955.
7. Burch, G. E.: Disturbances of water and sodium balance in congestive heart failure. Mod. Concepts Cardiovas. Dis. 17 (May) 1948.
8. Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections (report of Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis appointed by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association). Circulation 11:317 (February) 1955.
9. Page, I. A.: Atherosclerosis; an introduction. Circulation 10:1 (July) 1954.
10. Dry, T. J.: Present status of surgical treatment for cardiac diseases. J.A.M.A. 150:19 (September 6) 1952.
11. Fahr, G.: Pharmacodynamics of digitalis in congestive heart failure. Mod. Concepts Cardiovas. Dis. 14 (October) 1945.
12. Engelberg, C. D.: Treatment of cardiac arrhythmias. Arch. Int. Med. 95:123 (January) 1955.

Injuries of the Urinary Tract

F. TURNER REUTER AND FREDERICK A. REUTER*

George Washington University School of Medicine, Washington, D. C.

TRAUMATIC injuries of the urinary tract range between minor injuries which require only expectant management and major lesions which may require extensive surgical repair. One is faced with the problem of determining the extent of the injury because on this hinges the decision whether to follow the expectant or the surgical procedure. The extent of the injury can usually be determined by definite procedures and clinical study.

One must bear in mind that the urinary system is a series of reservoirs connected by conducting tubes. Any corrective procedure should have as its aim the restoration of this system with minimal scarring which later could cause strictures which, in turn, provoke infection and result in disabling sequelae.

Injuries of the Penis

Injuries of the penis which involve the urethra are fracture, dislocation and avulsion. They all, in one way or another, involve Colles' or Buck's fascia and are associated with deformity and swelling due to hemorrhage and urine extravasation. The treatment requires incision, drainage, and realignment of the urethra by the use of an indwelling splinting catheter, and, many times, diversion of the urine by cystostomy. Avulsion is a particularly complicated situation, which, in addition to the attention to the urethra, requires plastic consideration.

F. T. REUTER

F. A. REUTER

Rupture of the Anterior Urethra

Rupture of the anterior urethra results from a direct blow on the perineum forcing the

*Department of Urology, George Washington University School of Medicine, Washington, D. C.

urethra against the pubic arch. Injuries from a blow in the perineum involve the bulbous portion almost exclusively, while injuries from fracture of the pelvis affect the posterior urethra. The bulbous urethra is confined within the superficial perineal space which is closed above by the triangular ligament and below by Colles' fascia. Extravasated blood and urine therefore pass into the anterior portion of the perineum, and later extend beneath the dartos of the scrotum and upward over the abdomen upon the fascia of the muscles of the abdominal wall.

Treatment is to re-establish urethral continuity by splinting the urethra over an indwelling catheter threaded from above through a cystostomy incision to meet one passed from below, drainage of the extravasation area, and diversion of the urine by cystostomy. Should catheterization be easy, which would indicate only partial rupture, an indwelling catheter alone may be tried.

Injuries of the Posterior Urethra

The posterior urethra can be sheared off where it passes through the urogenital diaphragm by either muscular displacement or a bone fragment when there is a fracture of the pelvis. History of injury, the appearance of blood at the meatus, inability to pass appreciable amounts of urine with a distended bladder, inability to pass a catheter beyond the triangular ligament, roentgenographic evidence of a pelvic fracture, and evidence of extravasation of a contrast substance make the diagnosis possible.

Retropubic exploration will reveal urine, blood and debris which must be removed. Frequently the torn ends of the urethra are widely separated. The bladder neck and prostatic portion, having lost some of their attachments, move upward in the pelvis, away from the triangular ligament. The bladder should be opened and an attempt made to thread a Foley bag-type catheter through the divided ends of the urethra. Besides serving as a urethral splint, traction on the catheter after the bag is distended in the bladder serves to pull the bladder, prostate and proximal urethra downward and into somewhat normal relationship to the distal end of the severed urethra. Lateral fixing sutures may be placed to pass through the prostatic capsule and into adjacent structures. Continued catheter traction has some disadvantages and by placing sutures, traction need not be severe or continued. Suprapubic diversion of the urine should be maintained for 7 to 10 days. Retropubic drainage should be adequate.

The most desirable technic of urethral repair in such an injury is direct repair of the lacerated ends through a perineal approach. Because of the state of the patient or associated injuries it is frequently not feasible to place the patient in the proper position for a perineal procedure.

Rupture of the Bladder

The bladder may be ruptured by a minor fall or suprapubic blow when it is distended. It may rupture into the peritoneal cavity or extraperitoneal spaces. Extraperitoneal rupture is commonly associated with rupture of the membranous urethra by the same method. If the rupture is extraperitoneal, the radiopaque substance will commonly extravasate from the bladder into the perivesical planes near the bladder neck and a fair amount of the substance will be seen in the bladder.

If the rupture is intraperitoneal, on passage of a catheter a variable but small amount of urine will be retrieved. Measured amounts of fluid will not return completely unless the catheter has passed through the tear into the peritoneal cavity. Blood will be present and the radiopaque solution will appear spread out in the peritoneal cavity on a higher level than in a case of extraperitoneal rupture. Surgical exploration of the bladder and peritoneal cavity after treatment of shock, suture of all lacerations and suprapubic diversion of the urine for several days before allowing the bladder to close are the procedures to be followed.

Injuries of the Ureter

Because of its size, site and mobility, the ureter is seldom injured. It is at times injured at its juncture with the kidney pelvis in cases of renal trauma. The ureter is more often injured by gunshot or stab wounds, associated

with visceral involvement, and the ureteral injury is often overlooked until symptoms of urinary leakage or infection arise. There may be transient or microscopic hematuria, a mass in the flank, chills and fever, all of which might be ascribed to and masked by the visceral injury. It might be difficult to determine if the continued illness or exacerbation stems from the obvious lesions or from a ureteral source. One must bear in mind the possibility of a coexistent involvement of the upper part of the urinary tract.

Intravenous or retrograde pyelography is of great assistance under such circumstances. If it is shown that the ureter is merely nicked, one can evacuate the accumulated urine or pus from the flank and afford adequate drainage, or can pass a catheter to the kidney and down the ureter to the bladder to serve as a splint. If it is apparent that drainage will be unsatisfactory, a nephrostomy can be done, still using a splinting catheter.

Should the ureter be completely severed, an anastomosis over a splinting catheter can be done with a ureterostomy, pyelostomy or nephrostomy, while the anastomosed ureter is healing. Should a large segment of ureter have been blasted away, ureterocutaneous transplantation can be done if sufficient upper ureter remains. If not, a permanent nephrostomy or a nephrectomy can be done as indicated by the circumstances. One must be certain of the presence of a contralateral kidney before a nephrectomy is done.

If the ureteral lesion is adjacent to the bladder, reimplantation can be done provided sufficient length can be obtained, or, if the anal sphincter is intact neurologically, ureterosigmoidostomy can be done. In any event, drainage of the urine and blood from the retroperitoneal space is imperative.

If one or both ureters are ligated, crushed, divided or included in a suture accidentally in the course of a difficult pelvic operation, anastomosis can be performed or the ureter can be reimplanted into the bladder if a sufficient length of ureter is available. If the additional time for repair is not feasible, ureterocutaneous diversion or nephrostomy is the procedure of choice. Although deliberate ligation is the simplest procedure, it is not a desirable one. Deliberate ligation or nephrectomy should not be done until it has been determined that a kidney is present on the opposite side. If both ureters are ligated, immediate nephrostomy is imperative. In cases in which a pelvic operation has been performed, it is a good rule not to treat a patient for acute renal suppression until it has been shown that the ureters have not been injured. Cystoscopy and roentgenographic examination will afford the most positive evidence of ureteral injury.

Injuries of the Kidney

If it were not for hematuria, minor injuries of the kidney would often be overlooked and the kidney would heal without sequelae or obvious reduction in functional ability.

Major injuries of the kidney are associated with a variable degree of early shock from which a rebound can be expected with proper treatment. The patient usually passes from that state into a period of apparent improvement for several days only to return to more severe shock from which it might be difficult to recover. When the initial shock is severe and difficult to overcome, there is either a rupture of a major vessel of the pedicle or an associated visceral injury. Under these conditions, an exploratory operation cannot be postponed very long after major efforts have been made to support the patient. If initial shock is minimal or moderate and if the patient responds to specific shock treatment, time may be taken to estimate the extent of renal damage, and one can decide whether to employ expectant treatment or surgical exploration.

If roentgenographic examination discloses an extravasation of the radiopaque medium which does not extend beyond the renal parenchyma, it is advisable to keep the patient in bed for 10 days to two weeks after hematuria has ceased. During this period, chemotherapy should be used to prevent infection and secondary hemorrhage. If the examination reveals an unusually large renal shadow as compared with the shadow on the opposite side, it might indicate a rupture of the renal cortex and the large shadow might be due to a subcapsular accumulation of blood and urine.

This type of injury can heal without drainage if infection does not ensue. Whether or not to perform an exploratory operation and evacuate the subcapsular blood is a controversial question. It might be said that it would be simpler to evacuate the blood than it would be to have to perform a nephrectomy later.

If physical examination discloses a mass in the loin on the injured side, and if roentgenographic examination reveals extravasation of the radiopaque medium beyond the renal capsule, increased density of the flank and loss of the psoas muscle shadow, with or without displacement of the intestines to the opposite side, it would be evident that the kidney has been ruptured and that the flank is full of blood and urine. An exploratory operation would be imperative under such circumstances.

If one of the poles of the kidney has been torn away, suture of the lacerated surface might spare the remaining portion. If the kidney has been torn into several parts or fragmented, nephrectomy would be the operation of choice. If there is a choice of segmental removal or nephrectomy, the presence of the opposite kidney must be determined first.

The George Washington University Hospital

Cancer of the Brain: Newer Methods of Diagnosis and Treatment

JAMES W. WATTS*

George Washington University School of Medicine, Washington, D. C.

JAMES W. WATTS

CANCER of the brain used in the broad sense should include not only the few primary carcinomas and sarcomas and metastatic tumors but also most gliomas of the brain. While great advances have been made in the operative treatment of brain tumors, about half of the gliomas recur within a year. In his address at the opening of the National Cancer Conference in 1949, Dr. Charles S. Cameron, Medical and Scientific Director of the American Cancer Society, said: "There was a time, and it is within the memory of some who are still living, when cancer was the personal concern of but two professional disciplines—the surgeon and the pathologist. . . . Today, we can look backward on the cancer field and can see a change. . . . Many, yes, I shall say most, of the disciplines of science have seen their duty and have enlisted. . . ."[1] It is my belief that in the future greater progress will be made by looking on most gliomas as cancer of the brain and by enlisting the interest and support of all concerned to attack this problem.

Gliomas of the brain, which represent nearly half of all intracranial new growths, formerly were considered hopelessly malignant tumors. Impressed by the fact that many patients with tumors of this type survived for unexpectedly long periods, Bailey and Cushing[2] reclassified gliomas on a histogenic basis and correlated the prognosis with the histologic findings. They brought some order out of the chaos which had existed, and it is now possible to make a prognosis on the basis of the predominating cell type in the tumor.

MacCarty[3] reported the results obtained in 125 consecutive cases of glioma of the brain in which he has performed radical excision of the tumor or lobectomy since World War II. The hospital mortality rate was 8.8 per cent, the three year survival rate was 54.2 per cent, and the five year survival rate was 45.7 per cent.

Grant[4] made a survey of 1,733 cases of veri-

*Department of Neurology and Neurologic Surgery, George Washington University School of Medicine, Washington, D. C.

fied tumors of the brain. Of the 1,733 patients, 626 died either before or shortly before operation. In 534 cases, the patients lived five years or more after operation. In 84 of these 534 cases, the tumor was gliomatous (an astrocytoma or an oligodendroglioma). In cases in which the astrocytoma was situated in the cerebellum, the prognosis was better than it was in cases in which the tumor was situated in the cerebrum. Forty-seven patients with a cerebellar astrocytoma lived more than 10 years after the operation, and 41 of the 47 patients were able to return to work.

Sachs[5] made a study of 102 cases of metastatic tumor of the brain. The metastatic tumor was a sarcoma in 24 cases and a carcinoma in 70 cases. Five of the patients with metastatic sarcoma lived from one to five years after operation and one lived for 13 years. Ten of the patients with metastatic carcinoma lived from one to four years. Although less than one-fifth of the patients with a metastatic tumor lived as long as a year after operation, Sachs expressed the opinion that surgical removal is the best type of treatment for such tumors. Davidoff[6] found that the most common sites of primary tumors which metastasize to the brain are the lungs, breasts and kidneys.

Among the new procedures and agents that are used in the diagnosis and treatment of intracranial tumors are electro-encephalography, cerebral angiography, radioactive isotopes, betatron generated rays, chemotherapy, and combined hypothermic and hypotensive technics in anesthesia.

An electro-encephalogram should be made routinely in all cases in which the presence of a brain tumor is suspected. It is helpful in determining whether or not a tumor or other organic lesion of the brain is present. It also may indicate whether the lesion is focal or diffuse. Even if the electro-encephalogram suggests that a tumor is present, few surgeons operate on the basis of this evidence alone. They obtain a pneumoencephalogram, a ventriculogram, or an angiogram in order to determine the site of the tumor. However, an electro-encephalogram often helps one decide whether or not these methods of visualization by x-ray are necessary.

Cerebral angiography has improved the localization of intracranial tumors and has opened the field of cerebral aneurysms and vascular anomalies to surgical therapy. This important diagnostic procedure was introduced by Egas Moniz, who won the Nobel prize for his work in psychosurgery. Vascular tumors such as meningiomas, glioblastomas and metastatic carcinomas often have a circulation of their own. The vascular pattern of each of these lesions has certain characteristics which permit one to make a pathologic diagnosis in a majority of cases. Cerebral angiography is most valuable in cases of tumor of a cerebral hemisphere. In cases in which the presence of a metastatic tumor of the brain is suspected, the method is not accurate enough to cause one to deny the patients the benefit of an operation unless the angiogram discloses the presence of two or more neoplasms. Serial angiography, that is, the exposure of from four to eight films while the dye is in the cerebral circulation, has materially improved the value of angiography as it permits one to visualize the dye in both the arterial and venous phases.

The value of radioactive isotopes in the localization of brain tumors is being investigated. Peyton, Moore, French and Chou[7] have used radioactive diiodofluorescein for this purpose. After this substance is injected intravenously, the gamma activity over the patient's head is measured with a Geiger-Müller counter. These authors said that approximately 70 per cent of intracranial tumors can be correctly localized by this method alone. Selverstone[8] has studied the value of radioactive phosphorus when used for this purpose. The uptake of this radioisotope is much greater in cerebral tumors than it is in the normal brain. The radioactive phosphorus is injected intravenously, and the brain is probed with a cannula containing a Geiger-Müller counter.

An ingenious method of treating glioblastomas is being used by Farr, Sweet, Locksley and Robertson[9] at the Massachusetts General Hospital. Boron,[10] which has an affinity for tumor cells, is injected intravenously. The patient is then treated with the nuclear reactor at the Brookhaven National Laboratory. The

advantage claimed for this method is that the effective radiation is produced only at the site of interaction. They have not yet prolonged life but hope to do so with the aid of improved technic.

X-ray therapy has been effective in controlling many pituitary tumors. It often produces a striking temporary remission of symptoms in cases of medulloblastoma. In cases of other types of glioma, the value of x-ray therapy is doubtful.

Arnold[10] is employing rays generated with the betatron in the treatment of deep seated gliomas at the University of Illinois, and his results are interesting. He has reported that the rays can be controlled so that they produce the maximal effect on the white matter without injuring the cortex as they enter the brain. Because of the highly destructive nature of these rays, operation is performed in order to delimit the exact area of the tumor. Examination of microscopic sections has disclosed almost complete cellular destruction in the treated areas.

Triethylene thiophosphoramide, which commonly is designated as ThioTEPA, is being used in treatment of malignant tumors by Bateman[11] at the George Washington University Hospital. This chemical belongs to a group which includes nitrogen mustard, but it has the advantage that it does not produce some of the systemic effects caused by nitrogen mustard. It is injected intravenously and intramuscularly, and it also is administered intrapleurally and intraperitoneally. It brings about an increase in well-being and appetite and a decrease in pain, pleural effusion and ascites.

Adenocarcinomas of the breast and ovaries of human beings seem particularly sensitive to this drug. Temporary improvement occurred in three cases in which an adenocarcinoma of the breast had metastasized to the brain. Partial recovery of a paralyzed arm occurred in two of these cases, and vomiting was decreased in one case. In one case in which paraplegia was associated with an adenocarcinoma of the spinal column, laminectomy was performed and the administration of triethylene thiophosphoramide was started subsequently. The patient has continued to improve during the year since the administration of this drug was started. It has not been determined whether the primary lesion was situated in the prostate gland or in the kidney. In three cases of glioblastoma, the improvement has not been sufficient to warrant any conclusions.

Cerebral edema and hemorrhage are two of the chief handicaps to the neurosurgeon. Increased intracranial pressure makes a tumor difficult to approach, and it may be necessary to remove part of a lobe of the brain in order to expose the tumor. The difficulties are further increased when excessive bleeding occurs. In an effort to handle vascular tumors, Gardner[12] used induced hypotension to reduce blood loss. Decreased cerebral blood flow results in decreased oxygenation of the brain but there is no decrease in the cerebral consumption of oxygen.

In a preliminary report, Eccleston, Coakley, Alpert and Albert[13] said that the hazard of lowering the blood pressure is reduced by combining the hypothermic and hypotensive technics of anesthesia. Since hypothermia results in a marked reduction in oxygen consumption, this supplements the hypotensive technic by protecting the brain and by permitting the use of light anesthesia. The optimal temperature apparently is about 31° to 32° C., and the optimal blood pressure is between 70 mm. and 80 mm. As a result of our experience with the combined use of hypothermic and hypotensive technics of anesthesia at the George Washington University Hospital, we believe that it reduces the loss of blood, makes the operation somewhat less difficult to perform, and that the patients have looked better on the day after operation than we had anticipated.

Zimmerman[14] recently has expressed the opinion that the general pathologist has shunned the field of neurosurgical pathology because of the complexity of the intracranial neoplasms, the complicated terminology (astrocytoma, ependymoma, glioblastoma multiforme, medulloblastoma, oligodendroglioma and spongioblastoma unipolare) and the current concept of the need for a battery of difficult staining technics. If pathologists in

teaching hospitals believe this, the belief is probably shared by their colleagues in medicine, chemistry and endocrinology, and they turn away students who otherwise would be attracted to the study of neurosurgical pathology. This is an unfortunate situation.

We must find some way of maintaining the gains made by Bailey and Cushing and other investigators without brushing off our colleagues in other fields. Kernohan and Sayre[15] and other pathologists at the Mayo Clinic have attempted to simplify the classification by dividing gliomas into four grades. By grading the astrocytomas and by eliminating the terms astroblastoma and glioblastoma multiforme, they have attempted to bring it in line with the classification of other neoplasms of the body. They said that special staining methods are not necessary in routine work. While the impregnation methods and other special stains have been important in the development of our present understanding of tumors of the central nervous system and as a research tool, the diagnosis of most brain tumors can be made accurately with hematoxylin and eosin or other simple stains that are used routinely.

Summary

New methods of diagnosis and treatment of malignant tumors of the brain offer the hope of curing more patients and prolonging the lives of those who cannot be cured at the present time.

While neurosurgeons may justly be proud of their accomplishments in the treatment of meningiomas, acoustic neuromas and pituitary adenomas and with the long period of survival in some cases of astrocytoma or oligodendroglioma, they have little to offer patients with a glioblastoma, medulloblastoma or glioma of the brain stem. Some other method must be used to treat malignant gliomas.

Greater progress in the management of intracranial tumors will be made in the future if most gliomas are classified as cancer of the brain and if neurosurgeons and neuropathologists enlist the interest of other disciplines.

REFERENCES

1. Cameron, C. S.: Outline of the conference: Its background and its purposes. In: Proceedings of the First National Cancer Conference. New York, American Cancer Society, 1949, p. 3.
2. Bailey, P. and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenic Basis with a Correlated Study of Prognosis. Philadelphia, J. B. Lippincott Co., 1926.
3. MacCarty, C. S.: Surgical treatment of gliomas of the brain. J. Internat. Coll. Surgeons 23:290 (March) 1955.
4. Grant, F. C.: Notes on a series of brain tumors. J.A.M.A 153:22 (September 5) 1953.
5. Sachs, E.: Treatment of metastatic brain tumors. J. Internat. Coll. Surgeons 23:427 (April) 1955.
6. Davidoff, L. M.: Panel on tumors of the nervous system. In: Proceedings of the First National Cancer Conference. New York, American Cancer Society, 1949, p. 227.
7. Peyton, W. T., Moore, G. E., French, L. A. and Chou, S. N.: Localization of intracranial lesions by radioactive isotopes. J. Neurosurg. 9:432 (September) 1952.
8. Selverstone, B.: Experiences in localization of intracranial tumors with radioactive isotopes and the probe counter. (In press.)
9. Farr, L. E., Sweet, W. H., Locksley, H. B. and Robertson, J. S.: Neutron capture therapy of gliomas using boron[10]. Tr. Am. Neurol. A., 1954, p. 110.
10. Arnold, A.: Use of the betatron in the treatment of brain tumors: Observations on the effect of betatron radiations on the normal brain and on brain tumors. J. Internat. Coll. Surgeons (to be published).
11. Bateman, J. C.: Chemotherapy of solid tumors with triethylene thiophosphoramide. New England J. Med. 252:879 (May 26) 1955.
12. Gardner, W. J.: Control of bleeding during operation by induced hypotension. J.A.M.A. 132:572 (November 9) 1946.
13. Eccleston, H. N., Coakley, C. S., Alpert, S. and Albert, S.: A preliminary report on the combination of the hypothermic and hypotensive techniques. (To be published.)
14. Zimmerman, H. M.: Nature of gliomas as revealed by animal experimentation. Am. J. Path. 31:1 (January-February) 1955.
15. Kernohan, J. W. and Sayre, G. P.: Tumors of the central nervous system. In: Atlas of Tumor Pathology. Washington, D. C., Armed Forces Institute of Pathology, 1952, section X, fascicles 35-37.

Preparation and After-care of Older Patients Requiring Surgical Intervention

CHARLES W. THOMPSON*

George Washington University School of Medicine, Washington, D. C.

CHARLES W. THOMPSON

DURING the past 10 years there have been an increasing number of papers on geriatrics in the medical literature. Even though it is generally known that the aged individual can undergo the hazards of surgery with relative impunity, for the most part, the physician and surgeon remain reluctant to operate on the tremulous, ataxic or dyspneic older patient. Restoration or improvement in physiologic function should never be denied an older person. For example, the removal of a cataract and fitting with proper lenses can have great economic and therapeutic rewards. An incapacitating hernia, a diseased gallbladder, a localized area of bronchiectasis, and painful or bleeding anorectal complications are a few of the common complaints often neglected by the attending physician because the patient is "too old and hasn't long to live, anyway."

Cole[1] has pointed out that older persons tolerate elective major surgery nearly as well as do the young. However, an emergency operation on the poor-risk or older patient is attendant with at least three times the mortality rate of an elective procedure. Eversole[2] said that since 1900 the general population has doubled, but the number of persons more than 65 years of age has quadrupled. He pointed out that since there are more elderly people alive it is obvious that there are more elderly people sick. He further said that a person living to be 60 years old can expect to reach the age of 76. At 70, he should expect to celebrate his eightieth birthday.

The economics of these figures assume large proportions, for if these people are useless to society they must be supported. If they are incapacitated because of physical or mental disability, to their nonproductivity is added the expense of institutional care or at least the diversion of the energies of another individual. Ability to feed oneself and perform one's toilet relieves society of many man-hours of labor.

*Department of Medicine, George Washington University School of Medicine, Washington, D. C.

Even senility can be modified by restoration of the simple dignity of being able to care for one's excreta. So often those relegated to an upstairs back room not only are the victims of dampness of their clothing from encroachment of the prostate on the urethra or relaxation of the vaginal structures, but they also are aware of the embarrassment and disgust that the younger members of the household feel for them. The desire to be dry first manifests itself as a lusty scream in the first few days of life.

The golden opportunity is the first interview. This appointment should be made at the time of the day when the physician is not harassed and can devote at least an hour to what will certainly be a long and detailed medical history. At this moment, the preoperative care of the patient begins. Rapport and hope are established. The complete and careful physical examination may uncover much besides the expected arrhythmias, the pipestem arteries, and the ankle edema. Ill-fitting dentures or the edentulous mouth is often a cause of inanition, and should be corrected. One who is old and devoid of hope has no appetite for any of the pleasures of life.

It is our practice to admit these people to the hospital for five or six days prior to the day of operation. This familiarizes them with the personnel and the efficient orderliness of things. It helps dispel the fear in this age group that "one goes to the hospital to die." That few die of operation is shown in table 1.

While the patients are in the hospital before the operation, the basic laboratory studies should include a urinalysis, a complete blood count, and a determination of the cell volume per cent of the erythrocytes, the albumin-globulin ratio of the serum, and the values for the urea nitrogen and total protein of the blood. Anemia and disturbances in blood volume and serum electrolytes certainly should be corrected so far as possible.

Most hospitals are equipped with a flame photometer, which may be used for determining the values for the serum sodium and serum potassium. Preoperative determination of the values for these electrolytes is important in correcting existing deficiencies and serves as a base line for detecting the presence of electrolyte disturbances after the operation.

A roentgenogram of the thorax and an electrocardiogram also should be made before operation is performed. Pulmonary complications are very frequent after operation. In the

TABLE 1

PATIENTS 65 OR MORE YEARS OF AGE DISMISSED FROM THE SURGICAL SERVICE OF THE GEORGE WASHINGTON UNIVERSITY HOSPITAL IN 1954

OPERATION	FEMALES		MALES	
	Alive	*Died in hospital**	*Alive*	*Died in hospital**
Gynecologic	23	0	0	0
Neurologic	2	0	1	0
Ophthalmologic	9	0	6	0
Otolaryngologic	1	0	1	0
Orthopedic†	9	0	5	0
Proctologic	3	0	14	0
Thoracic	15	0	19	1
Urologic	18	1	77	0
General	55	2	75	1
For traumatic lesion	21	0	4	0
For malignant lesion	48	6	50	5
TOTAL	204	9	252	7

*None of the deaths occurred in the operating room.
†Exclusive of operations for fractures.

calcified, scarred, fibrosed and emphysematous lung, minor postoperative changes can be discovered only by comparing a thoracic roentgenogram that was made preoperatively with one made after the operation.

The preoperative electrocardiogram is of great value. In addition to the all too frequent myocardial damage which occurs while the patient is under anesthesia, it is becoming apparent that a routine postoperative electrocardiogram is useful in detecting electrolyte disturbances if it can be compared with an electrocardiogram that was made before operation.

There is evidence that if the value for the serum potassium is brought up to normal preoperatively and maintained at a normal level after operation the patient will have less pain and the need for narcotics will be reduced.[3]

During the time the patients are in the hospital prior to operation, the internist or surgeon should visit them frequently. Walking with the patient in the corridors gives invaluable information as to cardiac reserve. An increase in the pulse rate on such minimal exertion is an excellent warning sign. Observation of cardiac rate and dyspnea on a few steps can be reassuring to the surgeon or an indication for further attention to the cardiovascular system.

There is no single test that can measure the surgeon's innate judgment of a patient's ability to tolerate an operation. Questions arise which can be answered in a reassuring way.

While on these visits and walks in the halls, the surgeon should tell the patient that he might awaken in an oxygen tent and have a nasal catheter, stomach tube or urinary catheter attached to him. These are the patient's clear-thinking days and the postoperative cloudy state will not be further complicated by panic as he becomes aware of these strange instruments in or about him.

The patient should be weighed daily. Low-grade congestive heart-failure often is not recognized by the ordinary means. Occult edema in the magnitude of 5 to 8 lb. can be mobilized by a test dose of 2 cc. of MERCUHYDRIN®. This recognition and treatment of low-grade congestive heart-failure is the difference between a smooth and stormy operative and postoperative course. If necessary to ameliorate these abnormalities, the time of operation can be postponed.

The tolerance of the older patients to sedatives and narcotics is often very low. They have lived long enough to become hypersensitive to many things. Drugs indicated should be specifically and judiciously used.

Postoperatively, all tubes should be removed and parenteral feeding should be discontinued at the earliest safe time. Ambulation should be enforced. The use of a bedpan is interdicted. Over and above the indignity of moving one's bowels in a supine position are very dangerous physiologic disturbances which are incident to this maneuver and bring about myocardial infarction and pulmonary embolism. If bathroom privileges are not warranted, an order should be written that the patient should use a bedside commode or a bedpan on a chair.

Restraint in administering fluids intravenously is indicated. If an error is made, it should be on the side of dehydration rather than on the side of hypervolemia. The aging myocardium does not tolerate an overload of fluids. A urinary output of 500 cc., with any random specimen concentrating to a specific gravity of 1.018 or 1.020, is an indication of good renal function. A minimum of 20 mEq. of potassium chloride should be added to each liter of fluid administered if the renal function meets the above requirements. All output from suction and renal excretion should be replaced, plus about 1500 cc. of additional fluid.[4]

It is not our practice to prescribe antibiotics, unless an obviously infected operative field is encountered. Antibiotics can mask a serious infection in this age group. These people notoriously respond poorly to the usual signs of fever and leukocytosis. Tachycardia, ennui and somnolence are more often signs of infection.

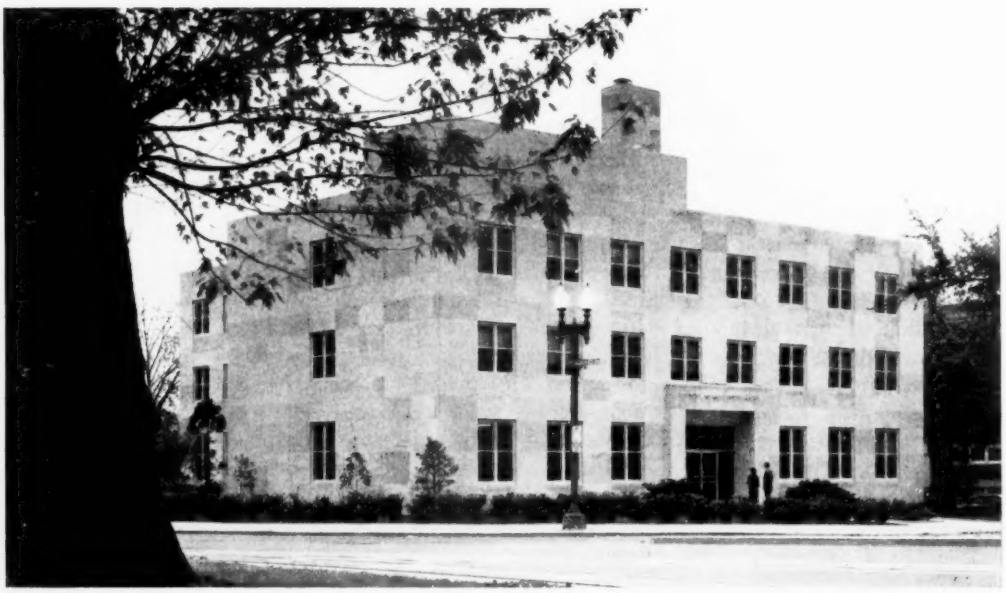
The written orders for the legs to be wrapped to the knees, and that the patient breathe deeply and cough, and that he move his legs freely in bed need no comment. Visits to the patient should be made several times a day.

Narcotics, as aforementioned, often have an untoward and unpredictable response in this age group. Because narcotics suppress the respiration, it is even more important to use them sparingly in patients of this age group in whom cardiac reserve and pulmonary gaseous exchange are often impaired. There are other measures that will relieve pain after operation. One of these is the implantation of a plastic tube at the site of the operation and the subsequent injection of an anesthetic solution through this tube as necessary to relieve the pain after operation. This procedure first was used in cases in which operations were performed on the thorax,[5] but it later was used in cases in which operations were performed on the upper part of the abdomen.[6] More recently, a modification of this procedure was used in cases in which operations were performed on the anorectal region.[7] In these cases, a plastic tube was inserted into the caudal canal, and an anesthetic solution was injected through the tube when necessary.

The postoperative care of elderly patients should not be left to the nurse's discretion. Decisions regarding the care for the succeeding 24 hours should not be made on the basis of rounds made only once a day. The freshly made bed and the neatly tucked-in oxygen tent should not be a deterrent to repeated and careful physical examination.

REFERENCES

1. Cole, W. H.: Operability in the young and aged. Ann. Surg. 138:145 (August) 1953.
2. Eversole, U. H.: Anesthetic management of the elderly patient. S. Clin. North America, June 1954, p. 619.
3. Thompson, C. W. and Parrish, A. E.: Unpublished data.
4. Alpert, L. K., Cotlove, E. and Parrish, A. E.: Fluid and electrolyte therapy. M. Ann. District of Columbia 22:536 (October) 1953.
5. Blades, B. and Ford, W. B.: Method for control of postoperative pain. Surg., Gynec. & Obst. 91:524 (November) 1950.
6. Gerwig, W. H., Jr., Thompson, C. W. and Blades, B.: Pain control following upper abdominal operations. Arch. Surg. 62:678 (May) 1951.
7. Gerwig, W. H., Jr.: Management of rectal and anal diseases. Am. Pract. 5:916 (December) 1954.



The George Washington University Cancer Clinic

Editorials

Postgraduate Medicine

Editor-in-Chief:
CHARLES W. MAYO, M.D.

Contributing Editor:
MORRIS FISHBEIN, M.D.

Executive Editor:
SYLVIA COVET

OVERTREATED FRACTURES

In the management of fractures it is common to err on the side of insufficient treatment. Inadequate immobilization of fractures of the long bones often results in delayed union and deformity. On the other hand, there are several common fractures which are too often overtreated, resulting in unnecessarily prolonged disability. In analyzing fracture treatment, two questions should be considered, especially where displacement is minimal: (1) Will failure to immobilize the fracture lead to displacement of the fragments and deformity, and (2) will failure to immobilize the fracture cause delayed union or nonunion? If both questions can be answered in the negative, the fracture may be adequately treated on a symptomatic basis. Immobilization should be applied as required to relieve pain, but active use and muscle rehabilitation should be instituted as soon as symptoms permit.

This discussion will include seven common fractures in which further displacement is not likely to occur after the initial trauma although immobilization is not applied. Furthermore, these fractures will heal satisfactorily without prolonged rigid immobilization, which therefore should be continued only as long as the painful symptoms require.

1. Fractures of the head and neck of the humerus are often comminuted and slightly or moderately displaced. Most of these fractures occur in elderly persons and are accompanied by swelling and extensive ecchymosis extending to the elbow. A hanging cast is not indicated in this type of fracture because the additional weight of the cast tends to cause the shoulder to dislocate downward due to the capsular damage and muscle weakness. This type of fracture is adequately treated by a sling and swathe. The arm may be removed from the sling for pendulum exercises a day or two after injury. Graduated active exercises are performed and the patient should be capable of 90 degree abduction after six weeks and almost full range of motion after 12 weeks.

2. Fracture of the head of the radius with severe comminution and displacement requires open operation and excision of the fragments. However, most fractures of the head of the radius have slight displacement. If there is marked distention of the joint, aspiration of

the hematoma under local anesthesia is indicated. The elbow should be immobilized for about 10 days and then active movement is permitted. Fractures of this type which may be considered borderline warrant a trial with conservative treatment. Occasionally such a case will require operative excision at a later date due to fibrous ankylosis or post-traumatic arthritis.

3. Undisplaced fractures of the patella may be transverse or stellate. It is important to determine that the quadriceps mechanism is intact by active extension of the knee against gravity or slight resistance. A cylinder cast is applied for a week or two and this is bivalved for application as required. The knee is splinted in extension for weight bearing but the splint is removed for exercises, especially of the quadriceps.

4. While fractures of the distal fibula involving the ankle joint require definitive treatment, fractures of the shaft of the fibula do not need rigid immobilization. Immobilization is required only for symptomatic relief, and weight bearing is resumed as soon as possible.

5. Fractures of the base of the fifth metatarsal are incurred by inversion of the foot and contraction of the peroneus brevis muscle. The more severe and painful fractures are best treated by a walking cast. However, many of these fractures are painful on weight bearing for only a few days. Firm bandaging with self-adhering bandage or with adhesive and gauze can be applied and worn with the shoe for about three weeks. The fracture line is visible for several months but it is safe to treat this fracture on the basis of clinical judgment rather than the x-ray appearance.

6. Fractures of the transverse processes of the lumbar vertebrae should not be referred to as "a broken back." If multiple processes are involved with considerable displacement, there is severe pain in the area of injury. Prolonged immobilization does not reposition the fragments or materially affect the healing process. The usual fracture of one or two processes with minimal displacement does not require plaster immobilization. Protective strapping will suffice.

7. Fractures of the pelvis are often multiple and there is usually slight displacement of one or both rami. Motion of the lower extremities is quite painful, especially where active adduction is involved. A pelvic binder may be applied if it adds to the patient's comfort. As a rule the support of the mattress is sufficient and limited motion of the extremities is permitted. Many of these patients can be lifted into a chair soon after injury, and this is especially important in cases of elderly persons. Weight bearing may be started on the uninvolved extremity, with gradually increasing weight on the injured side as it can be tolerated.

The importance of adequate treatment of fractures of the long bones should not be underestimated. However, the aforementioned types of fractures have often been observed to be overtreated, thereby prolonging the patient's disability. Where compensation insurance or public liability is involved, it is important not to overemphasize the degree of disability and the treatment. In the fractures which have been discussed, displacement of the fracture or delayed union has not been observed when treatment was on a symptomatic basis. It is as important not to overtreat fractures as it is to treat them adequately. Careful analysis of each fracture should determine the treatment which is necessary.

LEONARD T. PETERSON
Department of Surgery, George Washington University School of Medicine

OBSTETRICS AS A SCIENCE

OBSTETRICS is the most fundamental of all medical sciences. It deals with the very beginning of life. Therefore, research which leads to an understanding of early human development should pay greater dividends in better health for all of life. Why then has not more attention been focused on research problems in obstetrics?

The art of midwifery is as old as man, but science in obstetrics is very young. Van Leeuwenhoek's description of the spermatozoon

and Karl Ernst von Baer's discovery of the ovum occurred less than 300 years ago. Even after these basic revelations, another 100 years passed before it was realized that reproduction resulted from the union of these two human cells.

Obstetrics has been well represented in each era of medical advancement. Detailed descriptions of the pelvis and concern with the mechanics of childbirth accompanied the anatomic period. Oliver Wendell Holmes and Semmelweis pleaded for cleanliness in obstetric practice before Lord Lister and Pasteur produced proof of the benefits of antisepsis. Colebrook's bacterial studies clarified problems in puerperal sepsis and set the stage for the use of chemotherapeutic and antibiotic preparations in obstetrics. Streeter, Hartman, Corner, Novak, Ramsey, Hertig and Rock have added immensely to our knowledge of human reproduction through their contributions to placental and gynecologic pathology. In current psychosomatic medicine, obstetrics has a fundamental position.

Research in human reproduction is handicapped by inability to make animal comparisons. No other mammal has a placenta, a gestational period, food requirements, a posture, and certainly not an emotional pattern like those of man. Indirect comparisons are inadequate substitutes for direct experimentation. Research in obstetrics may seem small in comparison with other areas of investigation, but fortunately practically all scientific advances in medicine may be applied to the field of obstetric practice.

Scientific investigation has three components: a problem, an idea and a budget.

Solving such important problems in obstetrics as reversible hypertension of pregnancy, toxemia, the influences of nutrition and disease on embryonic development, and the responses of body tissues to the endocrine changes of gestation have far-reaching influences in other fields of medicine.

Ideas for productive research are born in an atmosphere of preparedness and practically always to those who have an intense interest in a problem.

Budgets are built from demonstrated needs and proper appeal. Unfortunately the young people most concerned with childbirth have the least economic ability to contribute to research. However, promising ideas about fundamental problems in obstetrics receive adequate financial support when they can be shown to have wide interest and implications.

There is a tendency in medicine to try to reduce experience and even experimentation to mathematical formulas. Flurries of figures presented as indistinct pellets on a distant screen should be backed up by facts. Certainly, accurate records leave a true impression of the past and point the way to progress in the future. Science in medicine represents the mechanics of producing facts, truths which stand proved in the space of time.

The practicing physician is a translator and transmitter of laboratory science to patient needs. The obstetrician has an opportunity to serve not only as guardian of the birth process, but also as a general physician and family adviser during an important and changing period in a woman's life. Although human reproduction is still accompanied by many imperfections, the application of modern science to obstetric practice has made childbirth safer and more comfortable for American mothers than ever before in the history of our nation.

JOHN PARKS
George Washington University School of Medicine

THE RHEUMATIC CROSSROADS

THE history of new remedies and new hopes for the control and prevention of arthritis and rheumatic diseases has been a continuous record of variation and uncertainty. Hundreds of new remedies have been proposed. None has succeeded in removing or completely arresting the underlying disease activity despite frequent initial encouraging results. Furthermore, the clinical methods for determining complete arrest of rheumatic activity are not available to us. Patients in a state of seeming remission may relapse at any time, and smoldering clinical progression of these diseases may occur in the absence of obvious symp-

toms. An exacerbation of acute rheumatic fever and rheumatic carditis following mitral commissurotomy has been frequently observed when no clinical signs of rheumatic activity had been noted for years prior to the operation. The positive existence of subclinical activity in the heart muscle with the characteristic Aschoff bodies has been encountered in approximately one-third of the pathologic specimens examined.

In 1949 the announcement of the cortisone effect on the rheumatic diseases electrified the world with hope. Physicians could visualize for the first time the likelihood of being able to maintain their patients both free of pain and economically secure despite persistent rheumatic activity.

The so-called side effects from steroid hormones were at first considered annoying deterrents to the ease with which the steroids could be employed. It is now recognized that 70 to 80 per cent of persons with chronically active rheumatic and arthritic disease cannot maintain steroid therapy in sustained dosage for longer than two years.

Side effects such as diabetes, hypertension, development of peptic ulcer, hirsutism, moon face, spread of hidden infection, demineralization of bone and collapse of vertebrae, intravascular clotting and attendant complications, psychiatric and psychologic abnormalities, potassium deficiency and sodium retention, and hypo-adrenia have been noted in a number of patients. To modify the undesirable consequences of use of the steroids, a reduction of dosage has been advised, but the advantage of low dosage steroid therapy is no greater than the effect of salicylates.

There have been other considerations of greater basic importance than the so-called side effects. Approximately a year following the introduction of cortisone therapy, a phenomenon was observed which was characterized by the apparent conversion of rheumatoid disease into a pattern similar in every detail to lupus erythematosus and periarteritis nodosa. In long-term cortisone-treated patients, recent reports have revealed x-ray evidence of progression of joint destruction which has appeared to be more extensive than one would expect to find in the untreated patient.

With the introduction of each new steroid, the advantages stated in preliminary reports have not been maintained with the passage of time. The relatively brief action of local injections in such chronic disorders, and the appearance of serious side effects even with the low dosages of the more potent compound, are indicative of questionable future value of the steroid approach in the management of the rheumatic diseases.

The physician responsible for long-term management can ill afford to embark on any form of treatment in rheumatoid disease where the initial advantage of pain relief may ultimately give way to late worsening or additional complications. An analogous situation would be the avoidance of narcotics in rheumatoid subjects for the reason that the effect of these drugs in such long-term chronic problems has often become more difficult to manage than the disease itself.

It would appear that we have arrived at the crossroads in the long struggle to effectively modify the relentless progress and the continuous damaging action of smoldering, uncontrolled rheumatic activity. We must choose between the continued direction of our attention and efforts toward a trial-and-error approach in symptomatic measures for the temporary relief of pain, and studies of the basic mechanism responsible for the rheumatic process, on whose basis a rational approach to treatment of a more lasting type might be developed.

Our particular research effort has been directed constantly toward the basic rheumatic process itself, and through this approach we have developed a new concept of mechanism. This concept has been useful in helping to explain the many bizarre features of the natural history and clinical behavior of the rheumatic diseases as well as the interrelationship between the various types. It has also revealed a new therapeutic direction which, during a six year period of application, has maintained our interest because of increasing evidence that it is possible to modify the rheumatic process at a primary level.

This concept is based on the fundamental

premise that rheumatic diseases in general represent an unusual form of tissue hypersensitivity reaction. In the past there have been ample pathologic data but little clinical evidence to support this hypothesis. Hypersensitivity reactions require the presence of both antigen and antibody. We have been conducting studies to determine, if possible, whether or not this antigen arises from a nonviable chemical source or a microbial agent.

The evidence collected through a variety of studies has indicated, contrary to current views, that the antigenic source may well be a tissue-invisible living agent capable of multiplication and responsible for the persistent chronicity of the rheumatic process. This source of antigen appears to be affected by certain antimicrobial and chemical agents, the broad-spectrum antibiotics, gold salts and other substances under investigation. It does not appear to be affected by penicillin and sulfonamide drugs.

A clue to the specific action of these substances on a hidden tissue-invisible antigenic source has been the selective development of flare phenomena associated particularly with the initial phase in the use of these agents. These induced flare reactions suggest the specific release of antigen and present a clinical counterpart of the Herxheimer phenomenon and the exacerbation of chronic brucellosis with certain anti-*Brucella* agents. These reactions are not due to drug sensitivity. When the various chemical and antibiotic substances are applied to the entire spectrum of the rheumatic diseases, the reaction is most intense in the severe forms of the connective tissue disorders, namely, lupus erythematosus disseminatus, periarteritis nodosa, ulcerative colitis, malignant rheumatoid disease and acute rheumatic fever. As little as 10 mg. of TERRAMYCIN® has been observed to promote a flare reaction in lupus erythematosus. Flare reactions are less marked in rheumatic conditions where constitutional features are minimal.

A parallelism between clinical and laboratory findings has been observed. Pleuropneumonialike organisms, which have received periodic attention since 1939 in discussions of etiology of the rheumatic diseases, have been isolated from the genital tracts of a number of our rheumatic subjects. These strains have been found to be differentially affected by all the substances which promote the flare reaction in connective tissue disorders. Two antimicrobial substances, penicillin and sulfonamide drugs, have no appreciable effect on these organisms. The substance which is most effective against pleuropneumonialike organisms in the culture media, Terramycin, promotes the most marked flare reactions in patients. AUREOMYCIN®, which is less effective in vitro, is better tolerated at the same or greater dosage levels in vivo.

Pleuropneumonialike organisms are invisible in inoculated tissues and in many respects behave like viruses. They pass filters which withhold visible bacteria, and their smallest reproducible size is in the range of the medium-sized viruses. The presence of these organisms in rheumatic tissues cannot be excluded by negative direct cultures at present because of known difficulties in cultivation on artificial media and inadequate knowledge of their growth requirements. It is possible also that the toxic resultant of the hypersensitivity reaction interferes with the initiation and maintenance of growth in cell-free media. Several strains have been isolated from sources other than the genital or respiratory tracts of our patients. These strains have not survived progressive subculture. One such strain was isolated directly from the joint fluid of an arthritic patient. Members of the same family of organisms which differ by their relative ease of cultivation have been isolated from certain animals and have been observed to produce arthritis in a species-specific manner. It is not surprising, therefore, that the human strains fail to affect any other species.

During the past seven years, on the basis of this indirect evidence, we have treated a number of rheumatic patients with the various agents other than gold salts found to be effective against pleuropneumonialike organisms in vitro. By carefully titrating the dosage of the particular substance employed, it has been possible to minimize the flare response and to note the gradual acceptance of progressively larger doses. By using this method over a long

period of many months or several years in the most chronic cases, we have observed improvement in the clinical status of our patients characterized by a gradual reduction in rheumatic activity and a trend toward correction of hematologic and blood chemical abnormalities associated with rheumatic activity. In a number of instances where remission has apparently become complete and fixed, withdrawal of the medication has been followed by sustained inactivity of the disease process.

The success of this form of management has been dependent on four main factors: (1) the recognition and full appreciation of the delicate balance in the rheumatic process; (2) a total approach to the connective tissue disorders and a recognition of the relationship between the various types; (3) direction of attention at all times to the fundamental concept of the mechanism which allows proper individualization in the management of each patient, and (4) a long-term view which is logically necessary in chronic disease. Although this approach appears promising, a final appraisal of its effectiveness must await statistical analysis of a sufficient number of patients with various types of rheumatic diseases followed for a period of at least five years. At present it is our belief that this approach is sufficiently suggestive to warrant intensive investigation.

While we contemplate our future direction at the rheumatic crossroads, would it not be well to spend some time in reflection on the clinical requisites which must be satisfied in any acceptable concept of mechanism? Cortisone has been observed to interrupt a variety of known sensitivity phenomena. Would not the initial dramatic effect of cortisone in rheumatic subjects be compatible with hypersensitivity as a basic phenomenon in these diseases? Would not the late worsening of many such cases under cortisone therapy suggest an increase in antigen which would ultimately render the block ineffective? Could not the rebound phenomenon following cortisone withdrawal be explained on the basis of a sudden reaction from the progressive accumulation of unneutralized antigen?

Could not the migratory aspects of rheumatic diseases be best explained as an expression of the immune mechanism? When the antigen-antibody reaction is most intense in one area, would it not be logical to surmise that the antibody level elsewhere might be lowered by the phenomenon of adsorption, with a reduction of the reaction tendency in other areas? Under these circumstances would we not expect migration of clinical signs of activity, the reaction being most intense at sites where antigen concentration is momentarily highest?

Might not the production of peptic ulcer from two chemically unrelated drugs, cortisone and phenylbutazone, represent another expression of interference with the immune mechanism rather than a so-called side effect? Peptic ulcer is four times more common in patients with rheumatoid disease than in those with unrelated conditions. Are we aware of the possibility that these observations may lead to a better knowledge of the nature of peptic ulcer?

Pleuropneumonialike organisms can be formed in vitro under certain conditions as bacterial variants from a variety of organisms which affect man, including the beta hemolytic *Streptococcus* and the *Brucella* organism. Could not the late smoldering phase of rheumatic fever be accounted for by the progressive sensitizing effect of the fixed-tissue, viruslike variant form of the *Streptococcus?* Could not the same mechanism hold for other organisms in other rheumatic conditions and arthritis, long after the removal of a primary focal infection? Could not physical or psychologic stress release antigen from a hidden source such as the reticuloendothelial system in the spleen and thus contribute to the mechanism of the waves and cycles of these diseases?

The answers to these questions must await future research, and this research is dependent on our decision of a direction at the rheumatic crossroads.

THOMAS McP. BROWN

Department of Medicine, George Washington University School of Medicine